Department of Neurology
Helsinki University Central Hospital

Department of Neurosciences
University of Helsinki

INFECTIONS, STROKES, AND BRAIN

– WHAT ARE THE OUTCOMES?

Terttu Heikinheimo-Connell

ACADEMIC DISSERTATION

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Supervisor

Professor Turgut Tatlisumak
Department of Neurology
Helsinki University Central Hospital
Helsinki, Finland

Institute of Neuroscience & Physiology
The Sahlgrenska Academy at the University of Gothenburg,
Gothenburg, Sweden

Department of Neurology
Sahlgrenska University Hospital
Gothenburg, Sweden

Reviewers

Docent Jaana Syrjänen
Department of Infectious Diseases
Tampere University Hospital
Tampere, Finland

Professor Pekka Jäkälä
Department of Neurology
University of Eastern Finland
Kuopio, Finland

Opponent

Professor Myles D Connor
Division of Clinical Neurosciences
University of Edinburgh
Edinburgh, United Kingdom

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To Tim, Oskar, Harri, and the warm heart of Africa.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which will be referred to in the text by their Roman numerals.

I Heikinheimo T, Putaala J, Haapaniemi E, Kaste M, Tatlisumak T. Leucocyte count in young adults with first-ever ischaemic stroke: associated factors and association on prognosis. *Int J Stroke*. 2015;10(2):245-250.

II Heikinheimo T, Broman J, Haapaniemi E, Kaste M, Tatlisumak T, Putaala J. Preceding and post-stroke infections in young adults with first-ever ischemic stroke: impact on short-term and long-term outcome. *Stroke*. 2013;44:3331-3337.

III Heikinheimo T, Chimbayo D, Kumwenda JJ, Kampondeni S, Allain TJ. Stroke outcomes in Malawi, a country with high prevalence of HIV: A prospective follow-up study. *PLoS One*. 2012;7(3): e33765.

IV Heikinheimo T, Chimbayo D. Quality of life after first-ever stroke: an interview based study from Blantyre, Malawi. *Malawi Med J*. 2015;27(2):50-54.

V Heikinheimo T, Salonen O, Elovaara I, Poutiainen E, Ristola M: Three-decade neurological and neurocognitive follow-up of HIV-1-infected patients on best-available antiretroviral therapy in Finland. *Accepted, BMJ Open. 2015*.

In addition, some unpublished data are presented.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
BDI	Beck Depression Inventory
BMI	body mass index
CAD	cervical artery dissection
cART	combined antiretroviral therapy
CI	confidence interval
CD4	cluster of differentiation 4
CNS	central nervous system
CRP	C-reactive protein
CT	computed tomography
DM	diabetes mellitus
EDSS	expanded disability status scale
FSS	fatigue severity scale
ICH	intracerebral hemorrhage
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C antibody
HIV	human immunodeficiency virus
hsCRP	high-sensitivity CRP
HUCH	Helsinki University Central Hospital
HYSR	Helsinki Young Stroke Registry
IL-6	interleukin-6
IRIS	immune reconstitution inflammatory syndrome
mNIHSS	modified National Institutes of Health Stroke Scale
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
MUAC	Mid Upper Arm Circumference
NEWSQOL	Newcastle Stroke-Specific Quality of Life Measure
OR	odds ratio
PCT	procalcitonin
PFO	patent foramen ovale
PI	preceding infection
PSI	post-stroke infection
QECH	Queen Elizabeth Central Hospital
QOL	Quality of Life

RSA	Republic of South Africa
SOMA	Stroke Outcome in Malawi
SSA	Sub-Saharan Africa
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VA	Verbal Autopsy
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organization
WMS-R	Wechsler Memory Scale

ABSTRACT

Background: Stroke is the second most common cause of death after cardiovascular diseases. Its prevalence in the young and middle-aged adults is increasing. Stroke is also the leading cause of disability worldwide. Especially in the young this is devastating due to their expected long lifespan. Low-income countries carry the biggest burden of growing numbers of stroke. In these countries infectious diseases play a major role in healthcare and well-being of patients. It is known that infections can trigger an acute stroke. It has not been investigated earlier how this affects the recovery from first-ever acute stroke in young adults.

Finland is an industrialized North European country with a high-income level and well-organized public health care. Around 20% of the Finns live in the area of the capital, Helsinki, and its surroundings. Acute stroke care in the Helsinki area has earned world-wide reputation due to its excellency. Human immunodeficiency virus (HIV) prevalence in adults is very low: a little over 3000 victims in a population of 5.4 million.

Malawi is situated in Sub-Saharan Africa (SSA). It is an agricultural country with main income coming from tobacco and tea farming, According to the World Health Organization, Malawi is among the countries with the lowest human development index ranking 170 out of 187 countries. Blantyre is the second largest city after the capital, Lilongwe. In SSA such non-communicable diseases as high blood pressure, diabetes mellitus, epilepsy, cardiovascular diseases, and stroke are increasing. Their treatment has been neglected due to other challenges in healthcare, like infectious diseases and high infant mortality. Stroke occurs more in SSA in the younger age than in developed countries. In Malawi, non-communicable diseases cause 28% of deaths. Malawi is also highly burdened by the HIV epidemic. The HIV prevalence among young adults (aged 15-49 years) is 12%. Stroke outcome has not been studied earlier in Malawi or its neighboring countries. Neither is it known, how HIV infection influences stroke recovery.

HIV and acquired immunodeficiency syndrome (AIDS) was recognized over 30 years ago. With the development of combined antiretroviral therapy (cART) during the mid-1990s the disease has changed from deadly to chronic condition with normal life span wherever good quality care is available. Although HIV-associated dementia (HAD) has become rare, HIV may cause milder neurocognitive impairments, which are called HIV-associated neurocognitive disorders (HAND) even with best available treatment.

Methods: The Helsinki Young Stroke Registry (HYSR) includes over 1000 patients aged 15-49 years with first-ever acute ischemic stroke, who have been treated in the Helsinki University Central Hospital. We investigated how inflammation

affects recovery after stroke. In the first study, we investigated the factors associated with high leukocyte count and its impact on the 3-month and long-term functional outcome in patients from the HYSR. We included only patients who had their leukocyte count measured within two days of the stroke onset. In a separate study, we evaluated how infections affected the outcome of stroke in young patients with first-ever ischemic stroke. We included both infections that occurred before the stroke i.e. preceding infections (PI), and in-hospital infections following the incidence i.e. post-stroke infections (PSI). Outcome was measured with modified Rankin Scale (mRS): if mRS was ≥2 it was considered unfavorable.

In Blantyre, we defined the characteristics and one-year outcome of first-ever ischemic or hemorrhagic stroke, and the impact of HIV infection on the stroke outcomes. The patients were diagnosed and treated in the Queen Elizabeth Central Hospital, which is the largest public hospital in the area. We included patients who arrived at the hospital within a week of the symptom onset. Their stroke severity was evaluated. Most patients underwent brain imaging and HIV testing. The patients were followed up for one year. The outcome was considered poor if mRS was ≥3. After 6 months or one year a selected subset of patients were interviewed about their quality of life with the Newcastle Stroke-Specific Quality of Life Measure (NEWSQOL).

In Helsinki, a group of HIV seropositive men were investigated three times: from between 1986 and 1990, in year 1997, very soon after the introduction of cART, and again in year 2013 in the Aurora hospital for infectious diseases. On each occasion they were invited for neurological, neurocognitive, radiological, and laboratory investigations to determine whether HIV infection has caused neurological or neurocognitive impairment following a very long follow-up with best available treatment. The Expanded Disability Status Scale (EDSS) was used to standardize the clinical neurological investigation. For neuropsychological examination several methods were used: subtests of Wechsler Adult Intelligence Scale (WAIS), and Wechsler Memory Scale-revised (WMS-r), list learning, fluency, Stroop and Trail – Making-B test. Depression was evaluated using the Beck Depression Inventory (BDI), and fatigue with fatigue severity scale (FSS). The three investigation-times were compared with relevant follow-up analyses.

Results: In Helsinki, 781 young patients from the HYSR were included in our study cohort of leukocyte count and ischemic stroke. Their mean leukocyte count was above the reference range: 8.8±3.1 x 10^9 cells/L (reference range: 3.4-8.2 x 10^9 cells/L). Dyslipidemia, smoking, peripheral arterial disease, stroke severity, and infarct size were associated with higher leukocyte counts. High leukocyte count was independently associated with unfavorable 3-month outcome even after adjustment for age, gender, and relevant risk factors. In the long-term follow-up (8.1±4.2 years) no association was found to the initial leukocyte count.

Included in HYSR, were 681 patients who fulfilled the inclusion criteria for our study about infections and ischemic stroke. Of these, 70 patients (10%) had PI, most commonly upper respiratory tract infection, and 103 (15%) had PSI, most commonly pneumonia. After adjusting for gender, age, and risk factors, both PI (OR 2.86; 95% CI 1.48-5.54) and PSI (OR 2.26; 95% CI 1.08-4.76) were independently associated with unfavorable 3-month outcome. Unlike PI, PSI was also associated with long-term (follow-up 7.8±4.0 years) higher risk of all-cause death.

In Blantyre, 147 adult patients with first-ever acute stroke were studied. The mean (±SD) age was 54.2 (±16.9) years. Among them, 26% had findings equivalent to intracerebral hemorrhage. Fifty (34%) patients were HIV seropositive. They suffered more often from ischemic stroke (89% of the patients with brain scan) than HIV seronegative patients. More than half (54%) of all patients had a poor outcome (severe disability or death) at 1-year, and the mortality rate was 45% at 1-year follow-up. Poor outcome was related to stroke severity and female gender but not to presence of HIV infection. HIV seropositive patients were younger and had less often conventional risk factors for stroke.

Twenty-five Malawian stroke patients were interviewed with NEWSQOL interview. Good functional outcome was positively associated with better QOL on the domains of ADL/self-care ($p < 0.005$) and ability for communication ($p < 0.05$). Females scored worse on the domains of fatigue ($p < 0.01$) and cognition ($p < 0.05$). Older age was associated with worse QOL on the domain of ADL ($p = 0.012$). Seven patients were HIV reactive. HIV infection did not affect the post-stroke QOL.

In Helsinki, the original 80 HIV seropositive patients were recruited to our study during 1986-1990, 23 were re-investigated in the 1997 evaluation, and 17 participated in the year 2013 evaluation. Fifty-three of the patients had died in the intervening years, 10 were not able to participate the study in 1997 or 2013. The median (range) age of this all-male group was 57 (46-79) when the latest evaluation was made. They were diagnosed HIV seropositive 27 (23 to 30) years earlier. Their CD4 nadir was 170 (4 to 408) cells/mm3 (reference range for blood CD4 count: 458-1406 cells/mm^3). They were on cART for 13 (5 to 17) years. A third (29%) of them had signs of polyneuropathy (EDSS>3), and nine (53%) suffered from fatigue (FSS>37). There were no clinical signs of central nervous system impairment. The neuropsychological follow-up showed no effect of HIV infection. In MRI there was a subtle increase in brain atrophy in two men, and another three had signs of lacunar ischemic stroke, some already seen in 1997. BDI showed mild depression in all three investigation time points (mean 4.65, 5.53, and 5.00, respectively).

Conclusions: The high leukocyte count was common in young stroke patients in Helsinki. It was associated with vascular disease and stroke severity. The high leukocyte count was independently associated with unfavorable short-term, but not with long-term outcomes. Both PI and PSI were associated with poor short-term outcomes. PSIs were also associated with higher long-term mortality.

In Malawi, more severe symptoms at the onset of stroke and female gender were associated with unfavorable 1-year outcome. HIV infection is common especially among young stroke patients in Malawi, but it does not worsen the outcome. However, it may be a risk factor for ischemic stroke for young people. Within specific domains, QOL after stroke was related to patients' age, gender, and functional recovery.

Despite more than two decades of HIV infection, the surviving and aging Finnish male patients had no describing features of HAD or HAND while on best available treatment. Polyneuropathy, fatigue, and mild depression were common, but more severe neurological features were absent. The amount of silent strokes in our HIV-infected subjects supports the results of studies about the virus increasing the risk of strokes.

TIIVISTELMÄ

Tausta: Aivoverenkiertohäiriöiden (AVH) esiintyminen nuorilla ja keski-ikäisillä on lisääntymässä. Ne ovat maailmanlaajuisesti merkittävin vammautumisen syy. Etenkin nuorilla, joilla pitäisi elämän olla vielä edessä, vammautuminen AVH:n seurauksena on katastrofaalista. AVH:t ovat myös toiseksi yleisin kuolinsyy maailmassa heti sepelvaltimotaudin jälkeen. AVH:n yleisyyden kasvaminen on nopeinta kehittyvissä maissa. Näissä maissa tarttuvat taudit muodostavat usein merkittävän haasteen terveydenhuollolle. Tulehdustautien tiedetään joskus käynnistävän AVH:öön johtavan tapahtumaketjun. Nuorilla AVH-potilailla ei ole tietääksemme aiemmin tutkittu, miten tulehdustaudit vaikuttavat akuutin AVH:n lyhyt- ja pitkäaikaisennusteeseen.

Malawi sijaitsee Saharan eteläpuolella, keski-eteläisessä Afrikassa. Blantyre on Malawin toiseksi suurin kaupunki. Maailman terveysjärjestön inhimillisen kehityksen indeksillä mitattuna Malawi sijoittuu 170. sijalle 187 maasta. Pitkäaikaiset tarttumattomat taudit, kuten verenpainetauti, epilepsia, diabetes, sydänsairaudet ja AVH:t ovat yleistymässä Saharan eteläpuolella. Näiden maiden terveydenhuollolla on paljon muitakin haasteita, kuten tartuntataudit ja korkea lapsikuolleisuus. Siksi pitkäaikaiset sairaudet jäävät usein huomioimatta. AVH:öön sairastutaan kehitysmaissa nuorempana kuin rikkaissa maissa. Malawissa pitkäaikaissairaudet aiheuttavat 28% kuolemista. Afrikan HIV-epidemia (human immunodeficiency virus) koskettaa Malawia. Nuorista aikuisista (15-49 -vuotiaista) 12%:lla on HIV-tartunta. Malawissa tai sen naapurimaissa ei ole aiemmin tutkittu AVH:iden ennustetta. Myöskään HIV-tartunnan vaikutusta AVH-potilaan ennusteeseen ei tiedetä.

Suomessa AVH:n akuutti hoito ja uusien tapahtumien ehkäisy on järjestetty laadukkaasti. HIV:n esiintyvyys on hieman yli 3000 tapausta koko Suomen väestössä. Lisäksi arvioidaan, että noin 1000 henkilöä ovat tietämättömiä tartunnastaan. HIV on tunnettu jo yli 30 vuoden ajan. Tehokas hoito siihen saatiin käyttöön vuoden 1996 puolivälissä. HIV-dementia on tehokkaan lääkityksen myötä käynyt hyvin harvinaiseksi. Kuitenkin tehokkaimmankin hoidon aikana osa potilaista kehittää dementiaa lievempiä kognitiivisia oireita.

Menetelmät: Helsingin nuorten aivoinfarktipotilaiden rekisteri sisältää tiedot yli tuhannesta 15-49 -vuotiaasta nuoresta aikuisesta, jotka ovat sairastuneet ensimmäistä kertaa akuuttiin aivoinfarktiin, ja jotka ovat hoidetut Helsingin yliopistollisessa keskussairaalassa vuosina 1994-2007. Kävimme läpi rekisterin potilaat ja arvioimme, miten tulehdukselliset tilat vaikuttavat aivoinfarktin ennusteeseen. Tutkimme, mitkä tekijät aiheuttavat aivoinfarktipotilaalla korkeaa valkosoluarvoa sekä miten se vaikuttaa nuorten aivoinfarktipotilaiden lyhyt- ja pitkäaikaisennustee-

seen. Otimme rekisterin potilaista mukaan ne, joiden valkosoluarvo oli määritelty kahden vuorokauden kuluessa aivoinfarktiin sairastumisesta.

Toisessa tutkimuksessa selvitimme, miten tulehdussairaudet vaikuttavat nuorten aivoinfarktipotilaiden ennusteeseen.

Malawissa halusimme selvittää sekä aivoinfarktin että aivokudoksen sisäisen verenvuodon piirteitä, selvittää AVH:n ensimmäisen vuoden ennustetta sekä sitä, onko HIV-tartunnalla vaikutusta ennusteeseen. Tutkimme myös elämänlaatua ja AVH:n vaikutusta potilaan elämäntilanteeseen. Potilaat hoidettiin Blantyren seudun suurimmassa yleisessä sairaalassa, Queen Elizabeth Central Hospital:ssa. Tutkimukseen otettiin potilaat, jotka olivat saapuneet hoitoon viikon sisällä AVH-oireiden alusta. Oireiden vaikeusaste arvioitiin ja useimpien potilaiden aivot kuvannettiin ja selvitettiin, onko heillä HIV-tartunta. Potilaiden toimintakykyä seurattiin vuoden ajan. Puolen vuoden tai vuoden kohdalla osalle potilaista tehtiin elämänlaatukysely NEWSQOL-haastattelulla (Newcastle Stroke-Specific Quality of Life Measure).

Helsingin Auroran sairaalan tartuntatautien poliklinikalla on seurattu ryhmää HIV-infektoituneita potilaita vuosina 1986-1990 sekä vuonna 1997. Kutsuimme heidät 2013 uudelleen neurologisiin ja neuropsykologisiin selvittelyihin sekä aivojen magneettitutkimukseen (MRI) ja laboratoriotesteihin, koska halusimme selvittää, vaikuttaako vuosikymmeniä sairastettu HIV heidän neurologiseen tilaan tai kognitioon. Käytimme EDSS-asteikkoa (Expanded Disability Status Scale) neurologisen kliinisen kuvan arvioimiseksi. FSS-asteikkoa (Fatigue Severity Scale) käytettiin väsyvyyden arvioimiseksi. Neuropsykologinen tutkimus sisälsi kaikkina kolmena tutkimuskertana useampia eri menetelmiä, muun muassa WAIS-älykkyystestiä (Wechsler Adult Intelligence Scale) ja WMS-R- muistitestiä (Wechsler Memory Scale – revised) sekä sujuvuutta, oppimista ja toimintakykyä mittaavia testejä. Aivojen MRI-tutkimusta verrattiin 1997 otettuihin kuviin.

Tulokset: Helsingissä 781 nuorten aivoinfarkti-rekisteriin kuuluvaa otettiin mukaan valkosoluarvo- ja aivoinfarktitutkimukseen. Heidän valkosoluarvonsa oli keskimäärin viitealueen yläpuolella: 8.8±3.1 x 10^9 solua/L (viitealue: 3.4-8.2 x 10^9 solua/L). Korkea kolesteroliarvo, tupakointi, ääreisverenkierron sairaus (kuten valtimokovettumatauti), akuutin vaiheen vaikeaoireisuus, ja aivoinfarktin suurempi koko nostivat valkosoluarvoa. Vaikka ikä, sukupuoli ja merkittävät riskitekijät otettiin huomioon, korkea valkosoluarvo ennusti riippumattomasti kolmen kuukauden epäsuotuisaa ennustetta. Akuutin vaiheen valkosoluarvo ei vaikuttanut AVH:n pitkäaikaisennusteeseen (seuranta 8.1±4.2 vuotta).

Nuorten aivoinfarktirekisteristä 681 potilasta soveltui tulehdus- ja aivoinfarktitutkimukseen. Näistä 70:llä (10.3%) oli aivoinfarktia edeltävä tulehdustauti, yleisimmin ylempien hengitysteiden tulehdus ja 103:lla (15.1%) aivoinfarktin jälkeinen tulehdustauti, tavallisimmin keuhkokuume. Sekä aivoinfarktia edeltävät (OR 2.86; 95% CI 1.48-5.54) että aivoinfarktin jälkeen (OR 2.26; 95% CI 1.08-4.76) sairastetut tulehdustaudit vaikuttivat epäsuotuisasti aivohaverin kolmen kuukauden ennus-

teeseen, riippumatta potilaan iästä, sukupuolesta tai tavallisimmista riskitekijöistä. Aivoinfarktia seuranneet tulehdustaudit huononsivat myös pitkäaikaisennustetta (seuranta 7.8±4.0 vuotta).

Blantyressa tutkimukseen otettiin mukaan 147 aikuista AVH-potilasta. Heidän keski-ikänsä oli 54.2 (±16.9) vuotta. Kuvatuista 26%:lla todettiin aivokudoksen sisäinen verenvuoto. HIV-infektio löytyi 50 (34%) potilaalta. Heillä iskeeminen aivoinfarkti oli yleisempi (89% kuvannetuista potilaista) aivokudoksen sisäiseen verenvuotoon verrattuna. Hieman yli puolella potilaista (54%) oli epäsuotuisa aivohaverin jälkeinen sairaudenkulku: he jäivät vaikeasti vammautuneiksi tai menehtyivät (45%) sairauteensa. Huono ennuste liittyi AVH:n akuutin vaiheen oireiden vaikeuteen ja naissukupuoleen, mutta HIV ei vaikuttanut ennusteeseen.

NEWSQOL-haastattelu tehtiin 25 aivohaveripotilaalle 6-12 kuukautta tapahtuman jälkeen. Suotuisa toipuminen liittyi potilaan itsenäisyyteen ja omatoimisuuteen ($p<0.005$) sekä kommunikaatiokykyyn ($p < 0.05$), korkea ikä heikensi elämänlaatua omatoimisuuden ja itsenäisyyden osalta ($p < 0.05$). Naiset kokivat enemmän väsymystä ($p < 0.01$) ja kognitiivisen tason laskua ($p < 0.05$). Haastatelluista 7 oli HIV-positiivisia. Sillä ei ollut vaikutusta elämänlaatuun aivohaverin jälkeen.

Yhteensä 80 suomalaista HIV-positiivista henkilöä otettiin tutkimukseen vuosina 1986-1990. Heistä 23 osallistui uudelleen tutkimuksiin vuonna 1997. Vuonna 2013, 17 miestä tutkittiin jälleen. Viimeisen tutkimuksen aikana heidän mediaani-ikänsä oli 59 (46-75) vuotta. HIV-infektio oli diagnosoitu 27 (23-30) vuotta aiemmin. Heidän vastustuskykyä mittaavat solunsa, CD4 lymfosyytit olivat alimmillaan 170 (4-408) solua/mm^3 (viitealue CD4 solut: 458-1046 solua/mm^3). He olivat saaneet cART-lääkitystä 13 (5-17) vuotta. Kolmanneksella miehistä (29%) oli polyneuropatiaan viittaavat kliiniset löydökset (EDSS >3). Yli puolet (53%) koki itsensä väsyväksi (FSS>37). Yhdellä potilaalla oli extrapyramidaaliseksi sopiva oireisto, muutoin kliinisessä neurologisessa tutkimuksessa ei havaittu keskushermostoperäisiksi sopivia oireita. Lakunaarisia aivoveritulppia löytyi kolmen HIV-potilaan MRI-kuvauksessa. Osa niistä näkyi jo 1997 tutkimuksessa. Kolmella potilaalla aivoatrofia oli hieman lisääntynyt verrattuna 1997 tutkimukseen. Neuropsykologisessa selvittelyssä ei havaittu kognitiiviseen sairauteen viittaavia muutoksia.

Yhteenveto: Nuorilla aivoinfarktipotilailla korkea leukosyyttiarvo oli tavallinen löydös. Verisuonisairaudet ja vaikea aivoinfarkti nostivat valkosoluarvoa. Korkea valkosoluarvo huononsi kolmen kuukauden ennustetta, mutta ei vaikuttanut pitkäaikaisennusteeseen. Myös tulehdustaudit huononsivat aivoinfarktin kolmen kuukauden ennustetta, mutta vain aivoinfarktin jälkeiset tulehdustaudit vaikuttivat potilaiden pitkäaikaisennusteeseen. Naissukupuoli ja vaikeat oireet huononsivat akuutin aivoverenkiertohäiriön jälkeisen vuoden ennustetta malawilaisilla potilailla. HIV-tartunta on tavallinen löydös nuorilla AVH-potilailla, mutta se ei vaikuta heidän ennusteeseensa. HIV-tartunta voi kuitenkin olla nuorilla aikuisilla aivoinfarktin

riskitekijä. Potilaan korkeampi ikä, naissukupuoli ja AVH:n jälkeinen toimintakyky vaikuttivat heidän kokemaansa elämänlaatuun.

Seurantatutkimuksemme mukaan yli kaksi vuosikymmentä kestänyt HIV-infektio ei altista Suomessa hoidettua potilasta HIV:in liittyviin neurokognitiivisiin ongelmiin eikä HIV-dementiaan, jos he ovat saaneet parasta tarjolla olevaa hoitoa. Vaikka polyneuropatia, väsyvyys ja alakuloisuus olivat tavallisia, keskushermostoperäiseen sairauteen viittaavia löydöksiä ei ollut. Pienen aineistomme aivoinfarktit tukevat muiden tutkimusten tuloksia: HIV on etenkin aivoinfarktien riskitekijä.

1 INTRODUCTION

Stroke is an important cause of death and disability worldwide. Its importance in the low-income regions of the world has been notified during the last few decades. The Global Burden of Disease estimates that more than 80% of the all stroke deaths occur in low- and middle-income countries.[1] The World Health Organization (WHO) defines stroke as: "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin."[2] The definition includes ischemic and hemorrhagic strokes as well as subarachnoidal hemorrhage. Ischemic stroke covers 80-85% of all strokes.[3] Etiology, risk factors, and outcome of stroke in young adults usually differ considerably compared to those seen in older individuals.

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) is one of the most commonly used etiologic classifications of ischemic stroke.[4] In TOAST, stroke etiologies are divided into five categories: 1) large artery atherosclerosis, 2) cardioembolism, 3) small vessel disease, 4) other determined etiology, and 5) undetermined etiology. Especially young patients often lack traditional risk factors or diseases that could trigger their stroke. These strokes are called 'cryptogenic'.

During the last two decades there are several studies that have evaluated the functional outcome and mortality of the young stroke patients. In the different studies, different types of strokes are included, all of them usually including ischemic strokes, but some also TIA or intracranial hemorrhages. The age-limits for young stroke and the definition of favorable outcome vary making it difficult to compare the studies to each other. The most widely used rating scales for functional outcome are the Barthel Index since year 1965 and modified Rankin Scale (mRS) of which original version was published in 1988.[5-7]

The role of infections as a cause of stroke and influencing the stroke outcome after stroke is highlighted more amongst the young stroke victims. This is because they have not developed the conventional risk factors yet. The burden of infectious diseases is even higher in developing countries where the stroke incidence is increasing.

The activity of HIV infection is measured with blood CD4 count and amount of HI-virus in serum. CD4 T-helper cells are a type of white blood cell. Nadir CD4 indicates the lowest blood CD4 count measured during the course of HIV infection. HIV has the potential to cause ischemic stroke especially in young patients.[8]

Predictions indicate that ischemic heart disease and cerebrovascular disease will overtake HIV/AIDS as a cause of death by 2030 in Sub-Saharan Africa.[9]

2 REVIEW OF THE LITERATURE

2.1 ISCHEMIC STROKE IN YOUNG ADULTS

2.1.1 Incidence of stroke in young adults

In the literature the cut-off age for the young adult in stroke studies varies from 40 to 55 years of age. Approximately 5-8% of all ischemic strokes occur in individuals younger than 45 years.[10-12] Above the age of 45 years the occurrence of stroke starts to increase exponentially.[13] Around one quarter of strokes are caused by non-conventional or uncommon causes. The proportion of young stroke victims is likely to be higher in low-income regions like Sub-Saharan Africa (SSA) where the overall mortality is high and stroke in general occurs at a 10 year younger age than in the Western world.

The most common cause of stroke is brain infarction. In young stroke victims, however, the proportion of hemorrhages, subarachnoid hemorrhage (SAH) or intracerebral hemorrhage (ICH), is greater (40–55%) compared to the general stroke population (15–20%).[14] In this review the analysis concentrates on ischemic stroke.

2.1.2 Risk factors of stroke in young adults

The traditional vascular risk factors, most commonly hypertension, smoking, diabetes mellitus (DM), dyslipidemia and obesity, accumulate with age and are more common in males in young stroke populations.[13] In developing countries, urbanization and increasing smoking rates are causing increased levels of strokes even in the younger generation.[15] Men are older when stroke occurs and often have clustering of multiple vascular risk factors.[16,17] In the young especially, smoking and dyslipidemia with high total and low-density lipoprotein levels, and low high-density lipoprotein level, are important risk factors (table 1). According to two recent large European young stroke registries, the most frequent vascular risk factors in the young are current smoking (49-56% of the patients), physical inactivity (48%), hypertension (36-47%), dyslipidemia (35-46%) and obesity (22%).[16,17] The vascular stroke risk factors are often less severe in this age group and have not yet caused severe damage on the cerebrovascular system or heart. Individuals younger than 40 years rarely have overt large-artery arteriosclerosis as a cause of their stroke.[18]

Table 1. Some factors in selected studies of first-ever ischemic stroke in young adults since the millennium from different continents.

Study period	Country	Pub. year[ref]	Age group/ mean age	Patients (men/women)	Smoking %	Alcohol %	Dyslipidemia %	HT %	DM %	OC (% of women)	Migraine
1994-1997	South-Korea	2000[19]	15-44 /34.4	149 (112/37)	51.0	31.5	8.1	38.3	10.1	2.7	2.0
1974-2001	Spain	2007[20]	15-45	272	49	31	17[a]	22	8	18	11
1988-1997	Norway	2004[21]	15-49	232 (136/96)	73.8[d]	NA	NA	35.8	11.2	NA	17.6
1997-2002	Switzerland	2005[22]	16-45/36	203 (108/95)	46	NA	39	19	2	22	0.9
2000-2006	Israel	2008[23]	18-45 /39.1	87	31.0	NA	18.4[c]	29.9	18.4	NA	NA
1994-2007	Finland	2009[24]	15-49 /41.3	1008	44.2	14.2	59.5[f]	39.1	10.4	17.9	17.2
2003-2008	Nigeria[g]	2009[25]	18-45	54 (26/28)	11.1	27.8	3.7[c]	77.8	11.1	4.1	0
1996-2010	Thailand	2013[26]	15-45 /35.9	85 (47/38)	38	14	4.7[c]	8.2	3.5	50.0	NA

DM=diabetes mellitus, HT=hypertension, OC=oral contraceptive use.
[a] Hypercholesterolemia, [b] Hypercholesterolemia or hypertriglyceridemia, [c] Dyslipidemia was defined based on complete lipid profile,
[d] Ever smoked, [e] Hypercholesterolemia or hypertriglyceridemia. Hypercholesterolemia only 19%, hypertriglyceridemia only 10%,
[f] High total or LDL cholesterol or low HDL cholesterol, [g] brain imaging was not done. NA indicates data not available.

Stroke is more prevalent in men than women in all age groups apart from those who are younger than 35-year-old and those older than 85 years.[18,27] Increasing age is increasing the risk of stroke markedly in early midlife, and in men.[13] Other non-modifiable risk factors are ethnic factors, low birth weight, and genetic factors like congenital hypercoagulopathy, sickle cell anemia, and occurrence of ischemic events in family.[27,28] Young people from black, and Hispanic races have a greater stroke incidence.[29,30] Sickle cell disease, in which 7 to 10% of affected individuals experience stroke before the age of 20,[31] and other single gene disorders as a cause of stroke often manifest at a younger age.[28]

Modifiable and well-documented risk factors, other than conventional risk factors, are dietary factors, obesity, physical inactivity, and postmenopausal hormone replacement therapy.[32] The risk effect of abdominal obesity seems to be higher in young stroke patients than in older, more than 65-year-old, stroke victims.[33] In Danish men, obesity (BMI ≥30 kg/m^2) was associated with a risk of stroke before the age of 55.[34]

Inflammatory processes and infections as a risk factor will be discussed later (2.3).

In women, puerperium, pregnancy, postpartum period, and oral contraceptive use increase the risk of ischemic stroke.[16,18,35] Migraine with aura prevalence and its female predominance in younger stroke patients supports the hypothesis of its importance in the pathogenesis of ischemic stroke in very young females. The absolute risk increase is low, and association between common migraine (migraine without aura) and stroke is not clear.[36] The under 35-year-old female stroke victims have often a physically inactive lifestyle.[16] Griffiths and Sturm have published a list of the other less common causes of stroke that are more common in women: "systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APLAS), central venous thrombosis (CVT), reversible cerebral vasoconstriction syndrome (RCVS), Susac's syndrome, Takayasu's arteritis, Moyamoya disease, Sneddon's syndrome, and fibromuscular dysplasia".[37]

The other risk factors are illicit drug use, heavy drinking and binge drinking, and short sleep duration.[16,18,35] Illicit drug use or drug abuse refers to recreational use of prohibited substances, like cannabis, cocaine, amphetamine, sedatives, opiates, and certain inhalants. The majority of all users are young. The use of injectable drugs makes the user vulnerable to infections. The link between stroke and drug use is strongest for cocaine and amphetamines.[38] Amphetamine abuse was associated with a 5-fold risk of hemorrhagic stroke and increased mortality. Cocaine abuse can cause both ischemic and hemorrhagic strokes. The most widely used drug, cannabis has not been confirmed as a risk factor for vascular events. However, there is a temporal relationship between its use and stroke in a study from New Zealand.[39] Binge drinking or acute heavy drinking is a risk factor for both ischemic and hemorrhagic stroke in young adults.[35,40,41]

Many young stroke patients remain without a definite cause or even a known risk factor for their stroke. On the whole, the interactions of several risk factors may be more important than a single risk factor since the simultaneous effect to the pathogenesis of ischemic stroke becomes more significant.[18] The accumulation of modifiable risk factors at the young age should lead to effective preventative measures already at the age group of adults in their 30s or even earlier.

2.1.3 Causes of ischemic stroke in young adults

Many vascular risk factors activate the vessel endothelium and thus cause inflammation leading to arteriosclerosis in the later age.[42,43] Consequently, large vessel atherosclerosis, atrial fibrillation, and small-vessel occlusion (TOAST categories 1-3) which are the main causes of stroke in general population, are less common in young stroke patients.[13] On the contrary, cervical artery dissection (CAD), vasculitides, coagulopathies, and hematological conditions (TOAST category 4, other determined causes of stroke) occur more in the younger population of stroke patients.

CAD is the most common cause of ischemic stroke in the young causing 15-24% of all the ischemic strokes in this age group.[22,24,44] According to a Finnish stroke study of dissection, CAD occurred as commonly in the internal carotid artery as in vertebral artery.[45] CAD in the multiple sites occurred in 13-16% of cases.[46] Many CAD remain without any symptoms.[47] The mean age of CAD patients is 45 years. Common predisposing factor for dissection is cervical trauma but many cases occur spontaneously.[48] Hypertension might increase the risk of dissection. Several genetic and environmental risk factors can possibly cause dissection. According to study by Pfefferkorn et al these patients might have generalized higher risk of inflammatory arteriopathy.[49]

The mitral valve heart disease is an important a cause of cardioembolic stroke in some populations while in others, like in many industrialized countries, it has virtually disappeared with an extinction of rheumatic valve disease.[18,37] This is causing, for example as many as 32% of cases of young ischemic stroke in Iran.[50] Often related to rheumatic valve disease but also caused by excessive alcohol abuse or other reasons, and causing 2-20% of the cardioembolic strokes in the young, is atrial fibrillation.[14,15,18] In South America a prevalent cause of cardiomyopathy, intramural thrombus, and cardioembolic stroke is Chagas disease.[51] Trypanosoma cruzi- protozoan causes this disease, also known as American trypanosomiasis, using blood-sucking insects as a vector.

Patent foramen ovale (PFO) is a remnant of the fetal circulatory bypass of the lungs. It is an opening between the right and left atrium. PFO is common, occurring in a quarter of the adult population. PFO is considered to play a role in ischemic stroke in the young, mainly when no other reason is found, but its role is still controversial.[16,37]

2.2 STROKE IN SUB-SAHARAN AFRICA

2.2.1 Introduction of Malawi and Sub-Saharan Africa

Figure 1. The map of Malawi. Source:http://www.norwich-dedza.org/images/malawi.gif. Reprinted with publisher's permission.

Malawi (Figure 1) is a landlocked country in central southern Africa; neighboring countries are Mozambique, Zambia, and Tanzania. One-third of the country is water, Lake Malawi. Malawi's main income source is agriculture, while the country's main exports are tobacco and sugar.[52] Half of the 15.9 million inhabitants of Malawi (51%) live below the national poverty line.[53]

Sub-Saharan Africa (SSA) is the term used to describe all of the countries that are located south of the Sahara (Figure 2). The population of SSA is 910 millions.[53] The annual population growth rate is 2.3% and the population is young: more than 40% is younger than 15 years.[54] SSA suffers still commonly of the high child mortality rate, infectious diseases including malaria, and malnutrition.[55,56] The southern part of the SSA is hit hard by the HIV/AIDS epidemic. The burden of disease in these countries, however, is moving from infectious diseases towards non-communicable diseases: contribution to the burden is increasingly in vascular diseases like stroke, high blood pressure or diabetes. The region is under health and demographic transition, which is caused by rapid urbanization, developing economy, and aging. The number of persons aged above 65 years is expected to increase by 15% in 2015. At present, 37% of the SSA population lives in urbanized areas.[53]

Figure 2. Sub-Saharan African countries (in green). Source: Connor MD, Walker R, et al. Burden of stroke in black populations in Sub-Saharan Africa. Lancet Neurol 2007;6:269-278. Reprinted with publisher's permission.

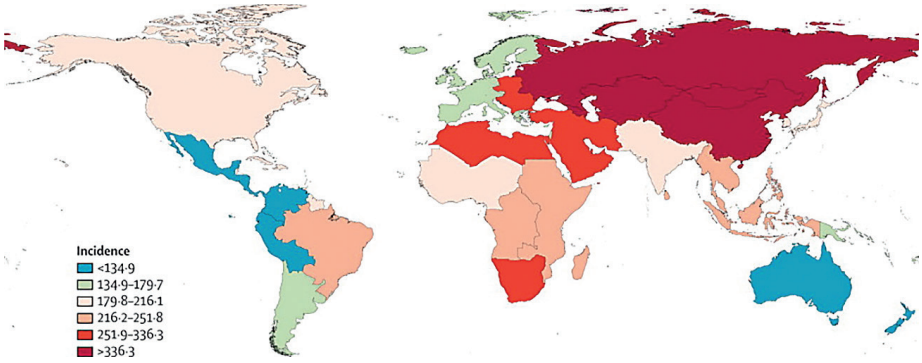

Figure 3. Age-standardized stroke-incidence per 100 000 person-years for 2010. Source: Feigin VL, Forouzanfar MH, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2014;383:245-254. Reprinted with publisher's permission.

2.2.2 Incidence of stroke in Sub-Saharan Africa

Despite the growing numbers of stroke patients in SSA (Figure 3), little is yet known about the incidence of the disease.[56,57] One of the first community-based studies in SSA occurred before the era of brain scanning, and took place in Ibadan, Nigeria. The study stuff was very small and the population of Ibadan very mobile, therefore, an underestimation is likely in the results of incidence of first-ever stroke (15 per 100 000).[58,59] The hospital-based stroke incidence studies easily underestimate the true incidence rate of the population. They have shown, however, a steady increase of the incidence. In Accra, the capitol of Ghana, stroke admissions were evaluated in three periods in 1960-68, 1976-83, and 1990-93 during which time total stroke admissions increased from 2% to 12%.[60] Further southern African studies from Zimbabwe and South Africa estimate the stroke crude incidence rate to be 31 per 100 000 (standardized to world population: 61/100 000) and 101 per 100 000, respectively.[61,62] Both studies showed marked age-related increase in the incidence. The comparison of these incidence rates with the rest of the world is difficult due to different study methods. In Finland the incidence rate for strokes have been one of the highest in the world (>2000/100 000 in 2002), but in recent decades there is a positive decline in this (more than 2% annually).[63] In middle to low-income countries the incidence has increased by 100% in first decade of this millenium.[64]

Recently, two further community-based studies were carried through: one in urban Nigeria, where the incidence was 25 per 100 000.[65] The other study in Tanzania, a prospective community-based survey, was done both in rural Hai and urban Dar es Salaam.[66] The incidence rates were 95 per 100 000 (95% CI 76.0–115.0) in Hai and 108 per 100 000 (88.1–129.8) in Dar es Salaam. When age-standardized to the WHO world population, the yearly stroke incidence rates were 109 per 100 000 (95% CI 89.0–130-9) in Hai and 316 per 100 000 (281.6–352.3) in Dar es Salaam. The Tanzanian study population was compared to the black population in Manhattan Stroke Study.[67] The rural Tanzanian population had similar incidence rate than urban black population in Manhattan while the incidence in urban Tanzania was substantially higher (Figure 4).

2.2.3 Features of stroke in Sub-Saharan Africa

In industrialized countries the prevalence of stroke is declining while in SSA it is increasing.[64,68] As SSA continues urbanizing and its population gets older, the prevalence of vascular diseases will increase. At present, the prevalence of stroke is lower than in developed countries but SSA stroke patients when compared with patients in wealthy countries have a less favorable recovery.[69,70] Age-adjusted stroke mortality is even higher than in the Western world.[57,71] Stroke is affecting people at a much younger age in SSA.[72-74] ICH is more prevalent in SSA and causes one third of the strokes (27-31%).[72,75,76] In a Senegalese study the proportion of

ischemic stroke was 65% and ICH 35%.[77] This proportion is higher than in any other part of the world. In a Tanzanian study the incidence rates of ischemic versus hemorrhagic stroke were similar to those in many developed countries: 83% and 17% respectively.[78] The scarcity of CT-scans in the region makes it difficult to estimate the stroke-type (infarction vs. hemorrhage) in many regional hospitals. Even when CT-scans are available, they frequently are out of order.

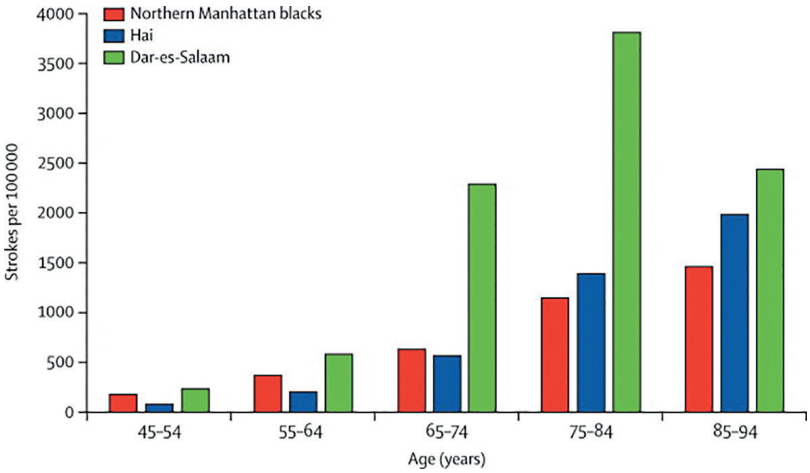

Figure 4. Age-specific stroke rates for people aged 45 years or over in Hai, Dar es Salaam, and black people in Northern Manhattan. Walker R, Whiting D, et al. Stroke incidence in rural and urban Tanzania: a prospective, community-based study. Lancet Neurol 2010;9:786-792. Reprinted with Publisher's permission.

When black people are compared with other ethnic groups, they have a higher prevalence of hypertension and at a younger age.[79] They are more likely to be salt-sensitive, have a low plasma renin activity, and low levels of aldosterone. Hypertension is, as elsewhere, a major risk factor for stroke in SSA.[72,76,80] Stroke caused by hypertension is thus the main reason for mortality and disability in SSA.[80] Diabetes is equally common in SSA as elsewhere.[57,68,75,80,81] Dyslipidemia is less common among black South African stroke patients.[75,81] Women are more commonly obese and men are smoking more.[68,82] The other significant risk factors in SSA are still prevalent rheumatic heart disease and other infectious diseases, poor nutrition and underweight, unsafe water, poor sanitation and hygiene, indoor smoke from solid fuels, and deficiencies of zinc, iron, and vitamin A.[83] Ischemic heart disease and large artery atherosclerosis, like carotid artery disease, are uncommon in the black African population though the incidence is expected to increase in the future.[66,75,80,84]

2.2.4 HIV and stroke in Sub-Saharan Africa

There were 35.3 million people living with HIV in the world in 2012.[56] SSA has by far the highest incidence and prevalence of HIV, with every 20th adult living with HIV. In SSA, hospital-based studies showed that ischemic stroke is more frequent than ICH causing 90% of HIV-associated strokes.[76,85,86] In South Africa, 6% of the admitted stroke patients were HIV-infected.[87] Stroke can often be the first manifestation of HIV infection in SSA.[85]

2.2.5 Quality of life after stroke in Sub-Saharan Africa

The quality of life (QOL) research evaluates the general well-being of individuals. Acute stroke lowers the QOL when causing to its victims disability and emotional stress like depression. In SSA the main research of post-stroke QOL were made in Nigeria and Tanzania.[88-90] Social and cultural differences are profound between the Western countries and SSA, yet in both regions QOL seems to be related with disability, depression, and anxiety.

One of the important factors for a stroke patient in the working age is whether they are able to return to their work and thus gain long-term economic independence. Many SSA countries have inadequate state-provided social security system and pension scheme. This makes people with disability very vulnerable. In a Tanzanian study, 68% of all-ages stroke patients gave up their work permanently.[88] Those returning back to work were significantly younger and had better 10-meter walk test time than those who were not employed. The post-stroke return-to-work-rates vary noticeably in different studies worldwide.[91] Typically about half of the patients return to work. In recent Japanese research 51% of the working age stroke patients returned to work.[92] One of the prognostic factors was the walking speed; others were no dysphasia, white-collar occupation and no attention dysfunction.

2.3 INFECTIONS AND ISCHEMIC STROKE

2.3.1 Definitions

Any signs of clinical infection or laboratory findings suggesting infection at stroke onset, or reported symptoms within the 4-week period before ischemic stroke define preceding acute or chronic infection (PI). Concerning post-stroke period, any acute infection occurring during the first few (5-7) days after the onset of stroke, defines post-stroke (PSI) or in-hospital infection.

2.3.2 Preceding infections (PI) and ischemic stroke

Chronic infections may increase the risk of stroke through a variety of mechanisms.[93] First, they can influence other risk factors like serum lipids. Infections can be a risk factor per se and act together with conventional risk factors and genetic predisposition. Second, they can damage vascular endothelium. Third, recurrent bacteremia triggers platelet activation and causes a procoagulant state. Chronic dental infections are associated with stroke in the young.[94,95] Chronic Chlamydia pneumoniae-infection and its antibodies are prevalent in both coronary heart disease and in young stroke patients.[96-98] HIV is discussed below (2.3.5. and 2.5.). Other pathogens have not been systematically studied in the young.

Important stroke triggers promoting strokes in patients of any age are acute infections, most commonly acute respiratory infection.[99-102] Stroke scientists have suggested several mechanisms of how infections trigger stroke: elevated antibody levels and other manifestations of inflammation reduce the amount of circulating antithrombotic proteins. Increased inflammatory markers like CRP, cytokines, or interleukins initiate extrinsic coagulation pathway, modulate anticoagulant pathway, and increase platelet activity.[103] The dysregulation of endothelium triggered by infection could initiate a thrombotic process: even minor infection can cause endothelial dysfunction in healthy children.[104] Contrast-enhanced high resolution MRI and positron emission tomography CT have demonstrated a vessel wall inflammation in patients with CAD.[49] PI is identified to have an association with CAD.[105] In patients with no other risk factors, acute infections are often associated particularly with cardioembolic or large-vessel stroke.[106,107] To prevent stroke, several methods are investigated: lipid lowering statins also having anti-inflammatory effects, and influenza vaccine.[108,109]

2.3.3 Post-stroke infections (PSI)

PSI is a frequent medical complication during the first few days after the insult in all age groups: the two most common types of infection are urinary tract infections which occur in 10%-29%, and chest infections in 11%-18% of the cases.[110-112] Factors like the severity of stroke, increasing age, treatment in intensive care unit, vomiting at stroke onset, having dysphagia, or using the nasogastric feeding tube make patients prone to infections.[112] These PSIs are one of the leading causes of death in stroke patients.[113-115]

An independent cofactor arousing PSIs is post-stroke immunosuppression. The activity of the immune system is modulated by the central nervous system (CNS) through pathways including the hypothalamic pituitary adrenal axis (HPAA), the vagus nerve, and the sympathetic nervous system.[110,114] An alteration of lymphocyte homeostasis exists: rapid T-lymphopenia and functional deactivation of T cells is a common phenomenon after stroke.[116] Sympathetic activity increases after stroke

making patients more prone to infections.[117] Polish researchers performed an interesting trial: they gave β-blockade to patients after stroke and this reduced the incidence of pneumonia.[118] By reducing sympathetic activity, the immunosuppression caused by stroke is reduced. The studies where early antibiotic therapy is given to the patient to prevent PSI have failed to show the benefit for the outcome.[119,120]

2.3.4 Infection parameters and stroke

Inflammatory markers serve as immune system health indicators. Systemic markers of inflammation are at the same time risk markers of stroke. During the admission of an acute stroke patient these markers are used to analyze and predict the risk of PSI. They give clues about the outcome of the stroke patient.[121] The used parameters should be accurate and easily available. Stroke patients have persistent signs of low-grade inflammation. It may mirror the ongoing atherosclerotic processes or reflect a chronic infectious disease. What needs to be proven is, however, that lowering of inflammatory indexes would lower the risk of stroke. In the following, some of the parameters are illustrated in greater detail.

In epidemiological studies an independent risk predictor for ischemic stroke and myocardial infarction is the increased leukocyte count.[43,121,122] It also detects the risk of recurrent vascular events.[123] Apart from acute or chronic PI, a high leukocyte count on admission is related to increased stroke severity and lesion volume, poor functional outcome, and an underlying atherosclerosis.[124] One of the various types of leukocytes, neutrophils, infiltrates the brain within the first 24 hours after acute stroke.[42,125-127] Neutrophilia associates with the volume of the ischemic lesion. The tissue injury in stroke activates microglia within minutes from the onset of ischemia and loosens the blood-brain barrier thus allowing macrophages to invade the CNS.[42]

C-reactive protein (CRP) is, at least in Finland, one of the most commonly used laboratory tests in the emergency unit. It is used for the detection of infection and inflammation. CRP is a hepatic acute phase protein which circulating levels of interleukin-6 (IL-6) are regulating. CRP and especially high-sensitivity CRP (hsCRP) are useful risk markers in routine assessment of cardiovascular risk in clinical practice. In first-ever ischemic stroke patients the baseline CRP-level detects the risk of a new stroke even more effectively than the risk of myocardial infarction.[128] CRP is a nonspecific risk marker predicting mortality in stroke as well as future vascular and non-vascular morbidity.[128-132] Levels of hsCRP increase with stroke severity and may be associated with mortality more than recurrence of stroke.[133] CRP is detected in atherosclerotic plaques.[134] It may contribute to atherogenesis and the procoagulant state. Statins and aspirin lower CRP-levels and these could be tools for anti-inflammatory treatment strategies for stroke patients.[135]

Another acute phase reactant at the interface between inflammation and coagulation is fibrinogen. Patients with a low plasma fibrinogen level indicate a

favorable functional outcome independently of patient's age, neuroradiological findings, or stroke severity.[136,137] The raised plasma fibrinogen level lowers with non-pharmacological treatment, such as cessation of smoking, a healthy diet or exercise.[138]

Cytokines are small proteins that are important in cell signaling. Interleukin-6 is a proinflammatory cytokine that helps to regulate immune reactivity, acute phase response, inflammation, oncogenesis, and hematopoiesis.[139] It is also synthesized for instance in stress, trauma, and tissue injury. After ischemic stroke, IL-6 levels are significantly elevated during the first 24 hours.[140] It has been used to predict the outcome after a stroke.[141]

Measurement of copeptin links with a release of vasopressin. This measurement detects early myocardial infarction. Procalcitonin (PCT) was first prescribed as a precursor for the calcitonin hormone. It is a biomarker that exhibits in greater specificity in bacterial infections.[142] After infection the PCT response is faster than CRP's, and it is the best parameter for identifying severe infection. In stroke, it predicts the risk of post-stroke respiratory tract infection but, however, this marker has low sensitivity.[143]

Among ischemic stroke patients the combination of markers predicted the patient's risk to develop post-stroke pneumonia or urinary tract infection: combination of WBC, CRP, and copeptin or procalcitonin measured on admission predicted the infection.[144] In a study from India: elevated hsCRP and IL-6 in acute ischemic stroke patients strongly correlated to functional disability 72 hours after the attack.[145]

2.3.5 HIV infection and stroke

In clinical series, 1-5% of HIV seropositive patients develop stroke. In the USA, admissions due to ischemic stroke in HIV patients have increased in nine years by 46%.[146] In another study from USA the incidence of stroke in HIV-infected persons was 5.27 per 100 person years compared to incidence rate of in non-infected persons 3.25 per 100 person years.[147] The difference was more significant in younger stroke victims and in women. No difference of incidence rates is seen in the hemorrhagic stroke ratios.[146] Usually stroke patients with HIV are young.[86,87,146,147]

Both HIV and its therapy increase the risk of ischemic stroke. The possible mechanisms of HIV-associated stroke are listed below (Table 2). In USA adults living with HIV when compared to general population are more commonly tobacco smokers.[148] In SSA HIV infection is not more prevalent with tobacco users. The other traditional atherosclerotic risk factors have relatively low prevalence in this patient group. But inevitably, due to the advent of highly active antiretroviral therapy (cART) since the mid-1990s, HIV seropositive people live longer and grow older, and are thus exposed to the conventional risk factors.[149] This will continue to increase the stroke incidence among the HIV seropositive patients.

Table 2. Possible HIV-associated causes of stroke[8]

Ischemic
HIV-associated vasculopathy
Associated with intracranial or extracranial aneurysm formation
Vasculitis caused by HIV
Accelerated atherosclerosis
Other disease of cerebral blood vessels associated with HIV infection
Opportunistic infection or neoplasia
Opportunistic infection causing stroke (tuberculosis, varicella zoster, syphilis)
Lymphoma
Cardioembolism
Bacterial endocarditis
Marantic endocarditis
HIV-associated cardiac dysfunction
Ischemic heart disease
Other causes
Coagulopathy (antiphospholipid syndrome)
HIV-associated hyperviscosity
Hemorrhagic
HIV-associated vasculopathy associated with aneurysm or vasculitis
HIV-associated thrombocytopenia
Mycotic aneurysm secondary to bacterial endocarditis

2.4 FUNCTIONAL OUTCOME AND MORTALITY OF STROKE

2.4.1 In young stroke patients with ischemic stroke

The prognosis in the young stroke patient is much better than in the elderly with lower mortality, lower recurrence rate, and better functional outcome.[24,26,150-156] However when the stroke patients are compared to their healthy age-mates there is at least 10-times higher risk of dying.[155-157] The risk of death is highest during the first month and the first year after the stroke in the young patients.[24,151,152] Usually deaths in young adults are caused by recurrent strokes (0%-33%), cardiac causes (13%-55%), and malignancies (23%-33%).[24,151,155,156,158]

In long-term follow up, from 3 to 12.4 years, most studies describe a favorable outcome (mRS=0-2) and independency in 68% - 87% of the young stroke patients.[22,26,150-152,154,155,157,159] On the other hand 3-5% of the study populations have remained with severe disability.[151,152] Milder handicap to severe disability is described between 14-27% of the patients.[155,157]

Of the unmodifiable risk factors, the young stroke patients' outcome worsened with increasing age and for the male sex.[154,155] In a Spanish study of the functional outcome of ischemic strokes, however, women who were 31-50-year-old had a worse functional outcome and higher mortality.160 In a Finnish assessment of 5-year mortality risk factors, sex did not affect the mortality but the older age of more than 45-years increased the risk of death.[24] In a Norwegian study of patients under 49 years of age, the age did not affect the mortality.[156]

Short-term mortality in a young stroke population is caused partly by the severity of stroke symptoms, when measured with modified National Institutes of Health Stroke Scale (NIHSS).[22,159,161] In the young, large-artery atherosclerosis was strongly associated with high risk of death and stroke of unknown etiology had significantly lower mortality.[24,151] Stroke caused by cardioembolism increases the risk of an unfavorable outcome and death in older stroke patients but among the young it was mainly related to short-term mortality after stroke.[24] In a Finnish survey, internal carotid artery dissection and bilateral ischemic lesions were independent predictors of a poor outcome.[161] The quality of acute stroke care affects the functional outcome of young stroke patients according to two surveys. One compared stroke care between Eastern and Western European stroke centers, and the other treatment differences between different racial groups in the United States of America.[29,162]

Diabetes mellitus predicts an unfavorable functional outcome or mortality also in the young stroke population.[22,24] From cardiovascular causes a worse functional outcome or mortality appears especially in heart failure and mitral valve stenosis.[24,26,158] An unfavorable outcome and mortality are related to risky lifestyle of alcoholism or binge drinking.[26,156,163] Another life-style risk factor that worsened the outcome in a Norwegian study was cigarette smoking.[156]

Seizures and epilepsy develop in to 6% of the surviving patients usually during the first year.[152,164] In ICH the risk of developing seizures is even higher: 7% of the patients after first year and 11% during five years follow up.[65] Epilepsy secondary to stroke is an independent factor causing an unfavorable outcome in the young.[156,165]

Stroke recurrence was at its highest during the first year: 1-4% of the patients and continues in a rate of 1% per year during the longer term follow-up reaching as high as 9% during a 6-years follow-up.[150-152]

Despite the fact that most stroke patients who are in working age, recover to be independent after stroke, only half of them (42%-69%) return back to work.[151,153,155,166] In recently published long-term follow up one young stroke patient out of eight surviving patients is not able to live independently even after 10 years from stroke.[167]

2.4.2 In Sub-Saharan Africa

The 7th most common cause of disability-adjusted life years (DALY) in southern SSA in 2010 were cerebrovascular diseases.[168] In SSA, only usually the most severe cases of stroke patients present to the hospital and are included to hospital-based studies. In Gambia, only eight stroke-patients out of 130 made a complete recovery during a one-year follow-up.[73] The functional outcome is rarely assessed in SSA stroke studies.

In many countries of SSA, death certificate data are often unavailable and vital registration systems are lacking, incomplete, or unreliable. Despite these difficulties, the Global Burden of Disease investigators estimated that in Africa, during 2004, occurred 424 673 stroke deaths (4% of all 11 200 000 deaths).[169,170] This estimation was based on the continent's existing records, census and survey models, and population-based epidemiological studies. From 1990-2010 in all SSA countries independently of whether they were rated as high, middle or low-income, the mortality-rates of stroke decreased significantly.[171] Cerebrovascular diseases as the leading cause of years of life lost in southern SSA in 2010 ranked 7th.[172] Verbal autopsy (VA) is a method of determining individuals' causes of death in populations coming from resource-poor settings with nonexistent vital registration system.[173] VA consists of an interviewer with a questionnaire, who interviews a person who knew the recently deceased person. Using the questionnaire the recent symptoms, signs, and characteristics of the deceased are collected to determine the cause of death. VA provides the only detailed mortality data for most SSA.[53] In the Tanzanian study where the mortality rate for both rural and urban area was estimated with VA, stroke was a cause of death in 6% of all deaths of the urban and rural regions.[174] In another VA-based study from rural RSA, 6% of all deaths were caused by stroke.[175] In a more recent Tanzanian study of 130 stroke patients, 24% died during the first month after the stroke and 60% during the 3-year follow up.[176] Older age and history of smoking were the only pre-stroke risk factors for case-fatality in this study. In a Gambian study, the mortality rates in one month and after a four-year follow-up were respectively 27% and 75%.[73] In this study, the initial stroke was the cause of death in 61% of the deaths. Unlike in high-income countries, where the post-stroke cardiovascular complications are relatively common, only one patient died of cardiomyopathy and none of myocardial infarction. In another Gambian study in-hospital and one year mortality rates were higher: 41% and 62% respectively.[71] In a recent Nigerian study of an urban population the one month case fatality rate was only 17%.[65] Overall, case fatality of stroke in Africa when estimated from hospital-based prospective studies, is about 30% during the first month post stroke, which is higher than the average 23% in much older populations in the rest of the world.[69,177]

2.4.3 In HIV patients

HIV seropositive young people, when compared to their HIV seronegative age-mates, are at higher risk of developing ischemic stroke.[85,147,178] In post-stroke HIV seropositive homosexual men the recurrence of stroke was higher than in HIV seronegative stroke victims.[179] HIV-related stroke patients' functional outcome and mortality needs a good clinical assessment.

2.5 LONG-TERM EFFECTS OF HIV INFECTION IN BRAIN

Before the development of combined antiretroviral therapy (cART) for HIV infection, it commonly caused severe cognitive disorders.[180-182] This wide range of neurocognitive complications fall under the acronym of HANDs (HIV-associated neurocognitive disorders).[183] This group of disorders is further divided into asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia (HAD). HAD associates with HIV-infection in the AIDS phase. Before the era of cART, the characteristics of HAD were the same as in sub-cortical dementia with notable clumsiness in motor function, behavioral changes, and loss of attention and concentration.[184] Since the start of the use of cART in high-income countries after 1996, HIV neurocognitive manifestations have changed, HAD has become rare. Even patients with long compliance and good response to cART can, however, suffer from HAND in milder forms.[184,185] About half of the patients on cART, continue to show performance levels lower than expected.[186] The characteristic HAND symptoms are less frequently subcortical. This clinical picture includes impairment in learning, in prospective memory, and in executive function; the pattern resembles neurodegenerative disorders like Alzheimer's disease.[181,185,187] The challenge is to differentiate these diseases in the aging brain.

The scientific community has suggested multiple possibilities for the causes of continuing high HANDs prevalence.[8,185,188] First, before the initiation of cART irreversible brain injury has developed already. Second, cART-treated individuals continue to show in the CNS HIV replication at low levels. This prolonged CNS inflammatory responses and neurotoxic viral proteins may result in neural injury or dysfunction; Prolonged CNS inflammatory responses are implicated in HAND pathogenesis. Third, development of HAND is linked to the history of low nadir CD4 (< 200 cells/mm^3). Fourth, some studies have suggested that better neurocognitive outcome corresponds to CNS-penetrating cART-regimes. Other studies, however, conflict with these; thus the role of these regimes is still controversial.[189] All cART-regimes benefit the brain by multiple mechanisms both systematically and in the CNS. Finally HIV patients may become exposed to other conditions that may affect cognition in long-term survivors, such as metabolic abnormality and associated vascular pathology or increased B-amyloid deposition in the brain.

3 AIMS OF THE STUDY

1. To investigate the factors associated with high leukocyte count and to its impact on short- and long-term functional outcome in young patients with first-ever ischemic stroke (I).

2. To study the effect of both preceding and post-stroke infections to the outcome in young patients with first-ever ischemic stroke (II).

3. To define the characteristics and the one year outcome of first-ever ischemic or hemorrhagic stroke, and the impact of the HIV epidemic on the stroke outcome in the Sub-Saharan country of Malawi (III).

4. To study the impact of stroke on the life situation and quality of life in post-stroke patients in Malawi (IV).

5. To learn how the HIV affects the long-term functional and cognitive status of HIV-infected receiving the best available treatment and care (V).

4 PATIENTS AND METHODS

The study consists of three parts: the first two publications, I and II, were carried out at the Department of Neurology, Helsinki University Central Hospital (HUCH), Helsinki, Finland, during the years 2011-2013. Publications III and IV are based on a research in the Medical Department, College of Medicine, University of Malawi, Blantyre, Malawi, during the years 2007-2010. The last work (V) was undertaken at the Department of Infectious Diseases, HUCH Aurora Hospital in the years 2013-2014. All the study protocols and procedures were approved by relevant local authorities in both participating centers, Helsinki and Blantyre.

4.1 DATA COLLECTION

4.1.1 Finnish young stroke patients (I, II)

HUCH serves as the only neurological emergency unit for patients who are independent in daily living. The catchment area population is 1.5 million. The Helsinki Young Stroke Registry (HYSR) includes all 15- to 49-year-old patients with first-ever ischemic stroke treated in HUCH between January 1994 and May 2007.[13] This registry defines ischemic stroke as an episode of focal neurological deficits with acute onset and lasting more than 24 hours, or lasting less than 24 hours with imaging evidence of an acute ischemic lesion. Patients were identified from the prospective discharge database of the hospital. Patients living in the defined hospital catchment area, and having discharge diagnosis of an ischemic stroke were included in the registry.

Our studies I and II are retrospective, observational, and based on the HYSR. The following stroke risk factors were recorded in both studies: hypertension, hypercholesterolemia, high fasting blood sugar and diabetes, smoking (≥1 cigarette a day), excessive drinking of alcohol (more than 200 g per week of pure alcohol), cardiovascular disease (coronary heart disease, heart failure, myocardial infarction, or peripheral arterial disease), and obesity (Body mass index ≥ 30 kg/m^2). Hypertension was defined as repeated blood pressure measurements of ≥140/90 mmHg.[190] Patients who were medicated for hypertension or who had a history of hypertension were defined as hypertensive. Hypercholesterolemia was defined as treated or total cholesterol level ≥5.0 mmol/L, low-density lipoprotein level ≥3.0 mmol/L, or high-density lipoprotein level <1.0 mmol/L (39 mg/dL). According to the WHO criteria, fasting blood sugar level of ≥7.0 mmol/L was considered high. Patients treated for diabetes and those who fulfilled the WHO criteria were

considered diabetic.[191] Stroke mimics and those who were lost to follow-up were excluded from our studies. TOAST was used for ischemic stroke subtyping.[4] Ischemic lesion size was estimated from the CT or MRI scan according to the largest lesion.[192] We used documented criteria, and categorized the lesions in to small, medium, or large and, if the lesion was situated in the territory of more than one main cerebral arteries, multiterritorial.

For the first publication (I) we reviewed the medical and laboratory data of all patients. The leukocyte count was measured from the blood sample drawn at hospital admission and analyzed in a central laboratory. We excluded patients who did not have this leukocyte count measured within the first two days from the onset of index stroke. Patients, whose count was less than 3.5 x 10^9 cells/L or exceeded 25.0 x 10^9 cells/L (outliers), were excluded to allow comparability with earlier studies.[123] We also divided the leukocytes into four quartiles: 1st quartile, <5.86 x 10^9 cells/L; 2nd quartile, 5.86 to 6.91 x 10^9 cells/L; 3rd quartile, 6.92 to 8.22 x 10^9 cells/L; and 4th quartile, >8.22 x 10^9 cells/L.

We analyzed the admission C-reactive protein (CRP) level and aural temperature (I). The laboratory reference for normal CRP was <5 mg/L during the study period. Fever was defined as aural temperature ≥38°C in both (I and II) publications.

For the second publication (II) we reviewed all the patient files with medical data and laboratory results. Preceding infection (PI) included any signs of clinical infection or indicative laboratory data at stroke onset, or reported symptoms of any infectious disease within the four-week period prior to index stroke. Post-stroke infection (PSI) included any acute infection occurring within seven days of stroke onset. These infections were further identified according to their site and character to the following groups: 1) Severe infections, including sepsis and endocarditis; (2) Chest infections, including pneumonia and pleuritis; (3) Upper respiratory tract infections including flu-like symptoms, sinusitis, bronchitis, and otitis media; (4) Genitourinary infections including urinary tract infections, pyelonephritis, and endometritis; (5) Gastrointestinal infections; (6) Skin and mucous infections including infections caused by foreign objects like iv-line, dermatitis, and otitis externa; and (7) Chronic PI, such as periodontitis or HIV infection. This study included those with multiple infections in different focuses or with both PI and PSI. Our study excluded as infections those with fever only or who were treated with a course of antibiotics, but did not have any clinical signs of infection. The study analyzed following inflammatory parameters; admission and the highest values of CRP, leukocyte count, and aural temperature.

The patients were followed up for three months. A structured interview of the patient, their next of kin, or carer was carried through by telephone for the long-term follow-up. The mean follow-up period was 8.1 ± 4.2 years in study I, and 7.8 ± 4.0 years in study II.

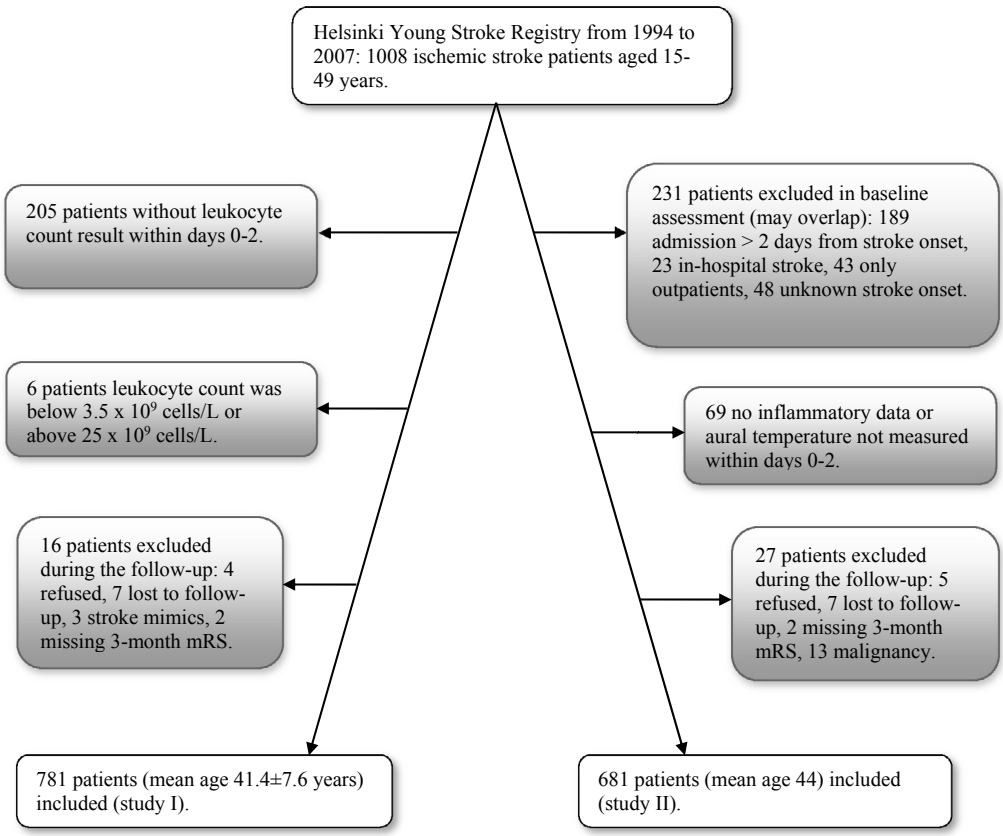

Figure 5. Flow chart for Finnish patients (I, II)

4.1.2 Malawian stroke patients (III, IV)

Our study took place in Queen Elizabeth Central Hospital (QECH) which is the biggest hospital in Malawi. Being the only public hospital for Blantyre region it is responsible for care from health center based care to the hospital-level. QECH also admits referred patients from other areas of Malawi. It is situated next to the University of Malawi, College of Medicine. It is a teaching hospital for clinical training of medical students. The population of the Blantyre-district is 1.5 million inhabitants.[193] Our study, the stroke outcome in Malawi (SOMA), was a prospective and observational study. The WHO definition of stroke was used: "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin."[2] This study included patients fulfilling the WHO definition, living within the defined catchment area, arriving at the hospital within a week of their stroke symptom onset, and giving consent (the patient or a next

of kin in case the patient was unable to). TIA-patients and patients with clinical signs of subarachnoid hemorrhage, trauma causing stroke, non-vascular cause for the stroke-like symptoms, or any concomitant severe disease were excluded from the study.

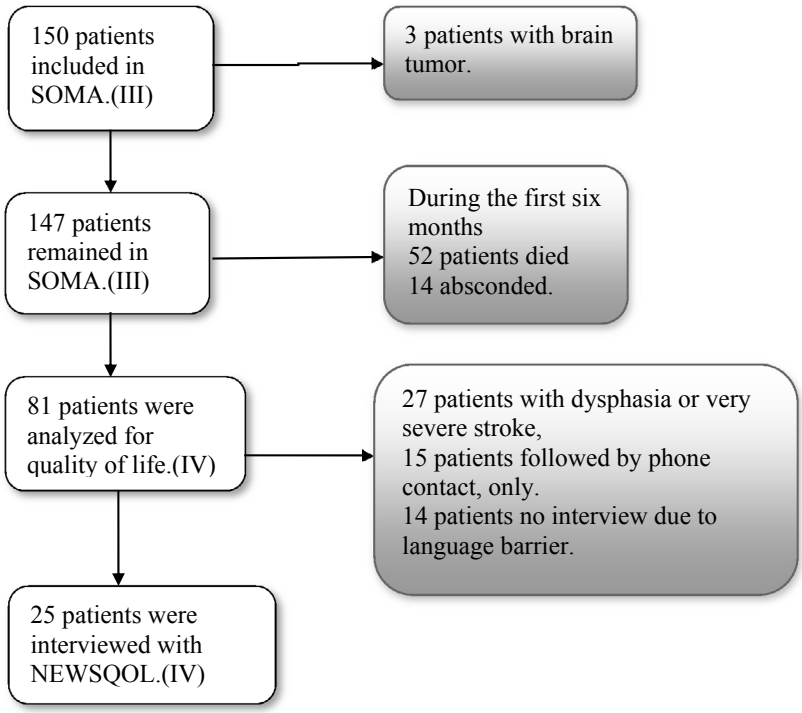

Figure 6. Flow chart of the Malawi patients (III, IV)

Our study patients were mainly recruited from the admission and medical wards of QECH. The admission ward is an on-call ward, where to patients are referred from the outpatient clinics, stay for a short-term, usually less than 24 hours, and are then admitted to the hospital or discharged. Using the information from the patient, their guardian, and patient's hand-held medical record as well as clinical observation and laboratory investigations, the following conventional risk factors were recorded: hypertension, hypercholesterolemia, and diabetes which were defined according to the WHO criteria as above. Obesity and nutrition were estimated using the mid upper arm circumference (MUAC). The nutritional status was estimated by measuring MUAC. The reference rate for adults is from 23 cm to 33 cm indicating normal nutritional values.[82] Other life style risk factors were recorded: smoking

(>one cigarette a day) and excessive drinking of alcohol (estimated more than 100 g alcohol a day, this definition is different from the Finnish studies I and II)). When available, we carried out CT or MRI of the brain. Most of the patients agreed with HIV-testing. The type of stroke was classified according to the Bamford criteria.[194] The patients were re-evaluated on the ward, at the outpatient clinic, or at their home six months and one year later. We conducted a telephone call for those who moved away or could not be reached physically.

In manuscript IV, patients recruited for SOMA and followed up for more than six months, were included. They were interviewed using a structured form (NEWSQOL, see below) for QOL assessment. We further asked questions about their post-stroke employment and accommodation. Due to its interview-based character, this study excluded those with severe dysphasia or who were still very ill. The interview was conducted either in English or in local language Chichewa.

4.1.3 Finnish HIV-seropositive patients (V)

This is an interventional follow-up study. We wanted to compare the changes in neurological and neurocognitive functions at least 25 years after onset of the infection. All patients had the HIV-1-type of infection. HIV seropositive patients were first recruited to this study between 1986 and 1990.[195-197] These all male HIV-infected patients have been treated and followed in the Aurora Hospital since the start of the HIV recognition in 1980. Aurora hospital is specialized in infectious diseases. HIV infection and AIDS are reportable diseases in Finland. Antiretroviral treatment is free for the patient. Altogether in year 1991, there were 248 patients with diagnosis of HIV attending the HIV clinic in Aurora. This made up two thirds of the HIV patients in Finland. In 1996 cART became available in Finland. In 1997 the surviving study population was re-examined.[198] In this follow-up the cognitive decline was relatively mild but brain atrophy had increased in the MRI analysis.[199] At present this cohort of HIV patients have lived with the disease for more than two decades. We included all HIV seropositive study subjects from the original cohort who were examined both in 1986-1990 and 1997, and who were willing to participate and signed the informed consent for the study. During the very first recruitment those patients were excluded, who had a history of CNS-disease or present HIV-related CNS-disease, if they had a marked learning disability, or prominent alcohol consumption.

Our study contained the neurological examination, neuropsychological investigation, laboratory tests, and MRI of the brain as the radiological investigation. The study registered from the patient's medical records and through conducting an interview, the level of education, and past and present employment. A detailed HIV history was taken and included: the estimated date of acquisition and date of diagnosis, the risk behavior group, history of antiretroviral therapy, CD4 count

at the time of diagnosis, nadir CD4, and HIV RNA. We analyzed all AIDS events, antiretroviral medication, the start of cART, and possible pauses of the use of cART. Our patients were further divided in groups depending if they had been in cART for more than 10 years or not and whether they had had a low nadir CD4 (<200 cells/mm^3) or not.

The study recorded from other medical history, cardiovascular diseases and events, metabolic diseases, psychiatric diagnoses, substance use (including alcohol and smoking), and medication. Patients completed a form of fatigue severity scale (FSS) to estimate the level of fatigue experienced (see 4.2.5).[200] The form was translated in to Finnish (Appendix 2).

For estimation of the nutrition we calculated the body mass index. Regarding the neurological examination of the patient, we tried to standardize the results with the use of neurostatus and EDSS (see 4.2.4).[201]

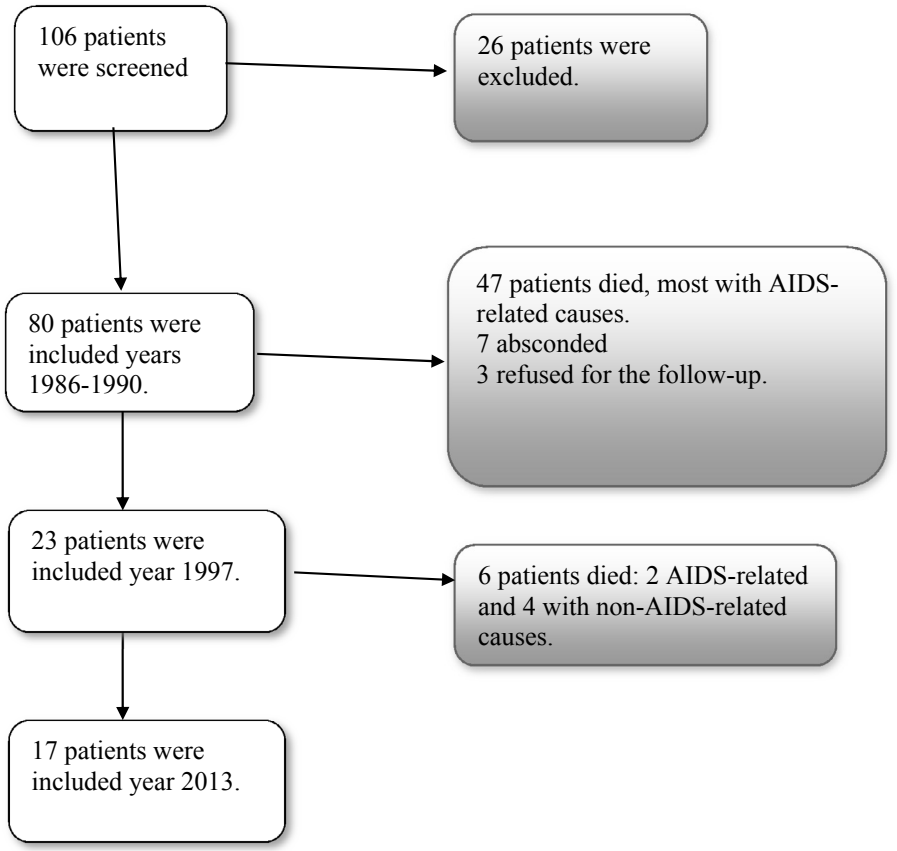

Figure 8. Flow chart of the follow-up study of Finnish HIV seropositive patients (V).

The neuropsychological examination included measures of mental flexibility (Wechsler adult intelligence scale WAIS/Digit Symbol; Trail-Making B),[202,203] memory (Wechsler memory scale WMS/Logical Memory I, II and Associative Learning ; List learning task; Complex Figure/retrieval),[204,205] language and related skills (WAIS/Arithmetic and Similarities), visual-spatial skills (WAIS-R/Picture Completion and Block Design ; Complex Figure/copying), motor skills (Tapping).[206] The mental state was evaluated using the Beck Depression Inventory/Short Form.[207]

Turning to laboratory assessment the following tests were obtained: a complete blood count, liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total bilirubin), kidney function (creatinine, protein in urine), plasma glucose, serum sample plasma lipids (cholesterol [total, HDL, LDL] and triglycerides), viral hepatitis serology (HBsAg, HBcAb, HCVAb, HCVRNA for HCVAb seropositives), syphilis serology from blood, electrocardiogram, plasma serum samples for possible neurological, metabolic and inflammation marker studies, plasma HIV-1 RNA, and blood CD4 count.

The brain MRI was performed on a 3.0 Tesla (T) MR unit (Philips, Achieva). The MRI protocol included conventional T2, FLAIR, T2*, DWI axial, T2 coronal, and T1 MPR sagittal images. The images were compared to the 1.5 T MRI pictures from 1997. The vascular degeneration was estimated using the Fazekas scale, where 0 denotes no signs of degeneration, 1=mild, 2=moderate, and 3 indicates severe vascular degeneration.[208]

4.2 OUTCOME PREDICTORS AND METHODS

4.2.1 Acute stroke severity: NIHSS and mNIHSS (I-IV)

The NIHSS is widely used in the western world to estimate the severity of acute stroke.[209] It is composed of 11 items, each of which gives 0-4 points. 0 score means no symptoms in that item and 4 means the most severe symptoms. In publications I and II, we considered the stroke-induced impairment assessed by NIHSS in the following way: 0-6 points categorized as mild, 7-14 as moderate, or ≥15 as severe impairment.

The NIHSS was adjusted for the SOMA (III, IV), because many Malawian patients do not know their age, which was asked in one of the items. The question of age we replaced by asking the name of the current president of Malawi (mNIHSS). Stroke symptoms were categorized as follows: mNIHSS 0-6 as mild, 7-12 moderate, 13-20 severe, and ≥ 21 very severe stroke symptoms.

4.2.2 Functional outcome: mRS (I- IV)

The mRS measures the degree of disability or independence in daily activities (table 3).[5] It is widely used for estimating the functional outcome after stroke. The bigger the mRS value the greater the dependency and disability. The scale is best assessed face to face, but can be assessed based on patient self-reporting as well as via telephone. In our studies I and II the mRS was categorized into two groups: mRS 0-1 indicating a favorable outcome and mRS 2-6 an unfavorable outcome. In our studies in Malawi (III, IV) the mRS was divided in three different categories, where mRS 0-2 was considered a good outcome in which patients were independent, mRS 3 was considered a fair outcome, where patients needed a little help, and mRS 4-6 was considered a poor functional outcome.

Table 3. Interpretation of the modified Rankin Scale.[6]

Score	Interpretation
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

4.2.3 Quality of life: NEWSQOL (IV)

NEWSQOL interview is composed of 11 domains and altogether 56 questions.[210] The domains are: Feelings, ADL/self-care, cognition, mobility, emotion, sleep, interpersonal relationships, communication, pain/sensation, vision, and fatigue (see Appendix 1). Every question or item has four options for a response. After a specific calculation every item gives a score ranging from 0 (worst QoL) to 100 (best QoL). NEWSQOL was translated into the local language, Chichewa.

4.2.4 Neurostatus and EDSS (V)

The functional status scale (neurostatus) and EDSS were developed to provide a standardized measure for global neurological impairment.[201] These are mainly used

when evaluating the impairment caused by multiple sclerosis. The neurostatus include functional systems (FS) of pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral (or mental). In our study we excluded cerebral domain because of the extensive neuropsychological examination where mental state was evaluated with Beck Depression Inventory.[207] Based on a standard neurological examination, the neurostatus rates the FSs as following: 0-1 means no symptoms, signs only, 2 mild symptoms and signs, 3 moderate symptoms and signs, and 4-6 severe symptoms and signs. The FS domains are used to determine patients EDSS together with patient's ability to walk (ambulatory). The clinical meaning of EDSS score is: 0-2.5 points means no or minimal disability, 3-3.5 moderate disability, 4-4.5 relatively severe disability but fully ambulatory, 5-5.5 severe disability and ambulatory 100-200 meters. 7-7.5 needs assistance for walking, 8-8.5 in wheelchair or bedridden but retains some self-care, 9-9.5 helpless and bedridden, and 10 meaning death.

4.2.5 Fatigue severity scale (V)

Fatigue is a prominent disabling symptom in a variety of neurological and medical disorders.[200] Fatigue severity scale (FSS) was developed to evaluate tiredness in chronic conditions (see Appendix 2). It measures of the disabling fatigue on daily functioning. FSS is a short questionnaire with nine statements, where the patient circles a number between 1 to 7, depending on how strongly he/she agrees with the statement. A high value indicates strong agreement and a low value strong disagreement to the statement. A total score of more than 36 (maximum 63 in most severe fatigue) suggests fatigue.

4.3 STATISTICAL METHODS

4.3.1 Studies I and II

We tested normality of continuous variables. The studies compared categorical variables with Chi-square and Fisher's exact tests. They compared normally distributed variables with Student's T-test and ANOVA. Furthermore, we used for non-normally distributed continuous variables Mann-Whitney U and Kruskal-Wallis tests. The binary logistic regression analysis was used to identify factors associated with an unfavorable 3-month outcome. After exclusion of patients who died within 30 days of the index stroke, a Cox proportional hazard model was constructed and adjusted for age and gender, and covariates known to associate with higher mortality in this patient population (age, gender, dyslipidemia, smoking, hypertension, cardiovascular disease, type 1 and type 2 diabetes, heavy drinking,

stroke severity and etiology, and lesion size). Proportionality assumptions for the Cox model were checked and no violations occurred. Two-sided significance was set at P<0.05. The statistical analyses were conducted using SPSS 19.0 for Macintosh.

For study I: the leukocyte count was analyzed both as a continuous variable and in quartiles. CRP was analyzed as a dichotomized variable: <5 and ≥5 mg/L. Multiple linear regression with forward stepwise entry was used for exploratory analysis on the baseline variables correlated with leukocyte count. In addition to age, gender, delay to leukocyte measurement, and all variables independently associated with higher leukocyte count, the adjustment in that analysis was based on univariate comparison between patients with favorable and unfavorable outcome with a criterion of $P<0.05$. The Kaplan-Meier log rank test served as the univariate analysis of the effect of baseline factors on the risk for endpoint events. Variables associated with a higher leukocyte count were additionally included in these models. Furthermore, to better rule out possible infection that may have emerged between stroke onset and admission, outcome analyses were subsequently adjusted for admission body temperature and CRP. Finally, we performed a sensitivity analysis on the main outcome interests by including only patients with leukocyte measurement on day 0.

For the study II: The model adopted to assess the 3-month outcome was adjusted for age and gender, and variables known to correlate with unfavorable outcome in this patient population in a univariate analysis (dyslipidemia, heart failure, peripheral arterial disease, smoking, heavy drinking, admission NIHSS score, etiology lesion size, lesion in multiple territories). Furthermore, the model was adjusted for the recorded inflammatory parameters, including the highest values of body temperature, leukocyte count, and CRP. PSI was included in the model investigating the effect of PI and vice versa. The Kaplan-Meier log rank test served for univariate analysis of the effect of preceding and in-hospital infections on the risk of long-term endpoint events. Since mortality was the only long-term outcome, in which there was a significant difference between the groups with or without PI and with or without PSI, only that endpoint was analyzed in a multivariate model. This model also included the same inflammatory parameters mentioned above.

4.3.2 Studies III and IV

Data were analyzed using the Statview™ and STATA™ for multivariate analysis. Descriptive statistics (mean, SD) were used to describe the baseline data. Standard error of the mean (SEM) was used instead of SD in study IV because of the small sample size. Proportions were compared by $\chi 2$ test and means by Student's t-test for normally distributed data, and the Kruskal-Wallis test for non-parametric data.

4.3.3 Study V

The neuropsychological parameters were analyzed using the parametric and non-parametric tests. The SPSS statistical software package was used for statistical analysis. Neuropsychological data were analyzed with multivariate analyses of variance (Manovas) and subsequent Anovas. The effect of age was controlled by Mancovas, and Ancovas Spreadsheets were used in the analysis of neuropsychological and MRI data.

5 RESULTS

5.1 FUNCTIONAL RECOVERY AND MORTALITY IN FINNISH YOUNG STROKE PATIENTS

The HYSR includes 1008 patients aged 15-49 years who experienced their first-ever ischemic stroke between January 1994 and May 2007. Out of the total number, 781 patients fulfilled our inclusion criteria for publication I. For study II, 681 patients from the HYSR fulfilled the inclusion criteria. Their mean age was 41.4 ± 7.6 years in both studies. In both studies, the male gender was more common: 62%.

5.1.1 Effects of leukocytosis (I)

Most of the stroke patients (75%) had their leukocyte count measured on the same day (day 0) of the stroke symptom onset. Patients with severe stroke symptoms (NIHSS≥15) sought medical help and were admitted earlier than patients with milder symptoms (Kruskal-Wallis $P<0.001$). The mean leukocyte count (8.9 ± 3.1 x 10^9 cells/L) was greater than the laboratory reference value (3.4 to 8.2 x 10^9 cells/L). The leukocyte count tended to decrease in patients who had delay in seeking treatment, but this trend was non-significant (ANOVA P=0.229).

Age and gender did not correlate with the leukocyte count. In exploratory multiple linear regression, the higher leukocyte count related to the higher NIHSS score (per point increase 95% CI 0.02-0.10, p=0.003), larger lesion size (95% CI 0.21-0.62, p<0.001), presence of multiterritorial lesions (95% CI 0.52-2.42, p=0.03), dyslipidemia (95% CI 0.04-0.89, p=0.031), cigarette smoking (95% CI 0.37-1.21, p<0.001), and peripheral arterial disease (95% CI 0.45-3.56, p=0.012).

An unfavorable 3-month outcome, mRS 2-6, was associated with older age (40.4 years versus 42.4 years, p=0.004). Other risk factors that were related with an unfavorable outcome in the univariate analysis were: preceding infection, heart failure, malignancy, and heavy alcohol drinking. Regarding stroke features, the following were correlating with an unfavorable outcome: severity of stroke (p<0.001), larger lesion size (p<0.001), and multiterritorial lesions (p<0.001). Patients with the following conditions had unfavorable outcomes: stroke etiology of large-artery atherosclerosis, high-risk source cardioembolism, or internal carotid artery dissection.

An unfavorable outcome (p<0.001) at three months was associated with a CRP ≥ 5. The higher aural temperature on admission did not affect the outcome (p=0.063). The leukocyte count was divided in to four quartiles: 1st quartile, <5.86 x 10^9 cells/L; 2nd quartile, 5.86 to 6.91 x 10^9 cells/L; 3rd quartile, 6.92 to 8.22 x 10^9 cells/L; and

4th quartile, >8.22 x 10^9 cells/L. A very unfavorable outcome (mRS 3 to 6) was strongly associated with the highest leukocyte count quartile. When CRP and body temperature were added in the analysis of outcome, the leukocyte count remained a significant predictor (odds ratio 1.12 per unit increment, 95% CI 1.04-1.12, *P*=0.003). Also, after a multifactorial analysis, in which demographics, risk factors, stroke severity and subtype, lesion size, presence of multiterritorial lesions, and delay to leukocyte measurement were included, the 3-month unfavorable outcomes were associated with the highest quartile of leukocyte count, when compared to the lowest quartile (OR 2.32 for 4th versus 1st quartile, 95% CI 1.32-4.09, *P*=0.003).

A high leukocyte count on admission did not correlate with long-term (8.1 ± 4.2 years) vascular endpoints: nonfatal or fatal ischemic stroke, composite vascular endpoint, or death from any cause.

5.1.2 Effects of preceding infection (PI), (II)

Of our study population, within four weeks prior to their stroke 10% had suffered from PI. The most common type of infection was upper respiratory tract infection (54%). The less common infections were those of lower respiratory tract (11%), skin and mucous membrane (11%), and gastrointestinal organs (12.9%). Our study population had only a few chronic infections (6%).

Patients with PI, compared to those without PI, had significantly higher CRP on admission (median 4 mg/L, intermediate range 3-23 mg/L vs 3 mg/L, intermediate range 3-6 mg/L, p<0.001). These patients with PI had higher values of CRP (median 12 mg/L vs 3 mg/L, p<0.001), highest leukocyte count (10.1 x 10^9 cells/L vs 9.1 x 10^9 cells/L, p=0.010), and highest body temperature (37.4°C vs 37.1°C, p=0.003). Some infection parameters measured on admission (the body temperature or leukocyte count on admission) were not associated with PI, however. The PI did not affect the length of stay in the hospital.

The only risk factor that was more common in patients with PI was heart failure (4.1% vs 11.4%, p=0.014). The other baseline variables in the univariate analysis were not associated with PI (TOAST, NIHSS, lesion size or territory).

In the multivariate analysis PI was independently associated with an unfavorable 3-month outcome (OR 2.86; 95% CI 1.48-5.54; p=0.002). In the long-term follow-up, PIs had no impact on any of the endpoints: recurrent ischemic stroke (log rank P=0.323), composite of vascular endpoints (p=0.157) or mortality (p=0.500) from any cause.

5.1.3 Effects of post-stroke infection (PSI), (II)

Of the included young stroke patients, 15% suffered from PSI. The most common focus in half of the patients with PSI (50%) was chest infection, of which most

frequently pneumonia. Genitourinary infections, most commonly urinary tract infection occurred in one third of the patients (35%). Patients who had PSI stayed for a longer period in the hospital compared to those, who did not have infections (20 days vs 10 days; p<0.001).

When compared with the young stroke patients without PSI, the conventional risk factors did not differ. History of migraine was slightly more common in patients with PSI (p=0.045). Their stroke characteristics were significantly different: they had more severe stroke symptoms (NIHSS 11 vs 3, p<0.001). In the brain scan, patients with PSI had significantly more frequently large infarction (64% vs 25%, p<0.001) and more often multiterritorial (11% vs 4%, p=0.002) or bilateral (42% vs 23%, p<0.001) than stroke patients without PSI. The main causes of stroke in patients with PSI were large artery atherosclerosis (compared to patients without PSI 13% versus 7%, p<0.001), high-risk cardioembolism (16% versus 10%, p<0.001) and carotid artery dissection (17% vs 7%, p<0.001). One third of all the included patients had a stroke of undetermined etiology (28% vs 31%).

Most of the measured parameters for infections were significantly higher in patients with PSI: admission CRP and leukocyte count, highest measured CRP, leukocyte count, and body temperature (for all: p<0.001). The only exception, which did not differ whether or not the patient had a PSI, was the admission body temperature (p=0.983).

In the multivariate analysis, after adjustment for demographics, risk factors, stroke severity, and subtype, lesion size, presence of multiterritorial lesions, and PI, patients with PSI exhibited higher risk for unfavorable outcome when compared to those without PSI (OR 2.26; 95% CI 1.08-4.76; p=0.031).

In the long-term follow-up, patients with PSI did not have increased risk of recurrent ischemic stroke (log rank p=0.124) or composite of vascular events (p=0.170). Nevertheless, they continued to have higher mortality rate after exclusion of those who died within 30 days (p=0.002).

5.1.4 Effects of infections in multiple focuses or both PI and PSI (II)

Four patients had PI in multiple focuses. This did not affect their 3-month outcome in the univariate analysis. Altogether 13 patients had PSI in multiple focuses. This increased significantly their risk of an unfavorable outcome (OR 5.2, 95% CI 3.07-8.8). There were 16 patients who suffered from both PI and PSI. They all had unfavorable 3-month outcomes.

5.2 STROKE CHARACTERISTICS, FUNCTIONAL RECOVERY, AND MORTALITY AFTER STROKE IN MALAWI

In QECH, 150 patients fulfilled the inclusion criteria and gave consent to the SOMA-study. Among them, three patients were excluded due to malignancy: one patient after the first brain imaging and two during the follow-up (Figure 6). The mean age of patients (53% males) was 54.2 ± 16.9 years. Almost all patients were independent before the onset of stroke (99% mRS=0-2). Hypertension was the most prevalent (55%) vascular risk factor, followed by diabetes mellitus (21%) and hypercholesterolemia (15%). Of the life style, smoking (18%) and heavy drinking (15%) were present. Electrocardiogram was recorded in 100 patients. It revealed in seven patients an atrial fibrillation. They were elderly patients (65.9 ± 12 years).

A brain scan was not done for 23 (16%) patients due to unavailability of the scan, CT or MRI. In the brain scan, 26% showed intracerebral hemorrhage (ICH). Most patients (87.5%) with ICH were hypertensive. The most common stroke type according to the Bamford criteria was partial anterior circulation stroke. Of them, 36% had left hemisyndrome. The majority of patients (53.5%) had severe stroke symptoms when admitted to QECH. Stroke severity was strongly associated with older age but not with gender.

The mortality rate at six weeks was 28%. Most of them (22%) died during the first admission. The cumulative mortality rates at six months and one year were 39% and 45%, respectively. Older age (58.5 ± 16.6 vs 54.1 ± 15.4 years, p=0.013), female gender (55% females vs 37% males, p=0.035), and stroke severity on admission (mNIHSS ≥ 13, 60% mortality vs mNIHSS 0-12, 23% mortality, p<0.0001) were significantly related with higher mortality at one year.

At one year, 47% of the study patients had a good or fair outcome (mRS=0-3). Similarly, the mortality, and a poor outcome was associated with older age, female gender, and severe stroke at presentation. In multiple logistic regressions other independent determinants of poor functional outcome at one year were the female gender (OR 2.3 95% CI 1.0-5.5, p=0.05), and stroke severity at presentation (mNIHSS ≥ 3 OR 4.5 95% CI 1.7-11.8, p=0.002). During the one-year follow-up, 11 patients had a recurrent non-fatal stroke. Secondary to stroke two patients developed epilepsy, and one of the stroke patients developed thalamic pain syndrome.

5.2.1 Stroke characteristics in HIV seropositive patients and effect of HIV infection to the outcome (III)

HIV seropositive patients formed one third (34%) of all the patients. They were significantly younger when compared to HIV seronegative patients (39.8±12.4 vs 61.9±14.0 years, p<0.0001). The majority of those below 55-years of age (65%) had HIV infection compared to those older than 55-years of whom 10% were HIV

seropositive. In our study population HIV infection was equally common in both men and women. They were less likely to have vascular risk factors like hypertension (24% vs 75%, p<0.0001) and diabetes (6% vs 25%, p=0.004). The HIV seropositive patients had more commonly anemia (11.8 ± 5.8 g/dl vs 13.6 ± 2.5 g/dl, p=0.0003). From the whole study population in 15 patients, of which five were HIV seropositive, presented with positive serological test suggesting syphilis (rapid plasma reagin).

Less common in HIV seropositive patients when compared to HIV seronegative stroke victims was ICH (11% vs 34%, p=0.004). Stroke severity was not associated with HIV status. There was no difference in MUAC between HIV seropositive and HIV seronegative patients (26.4±3.8 cm vs 27.3±4.2 cm). HIV seropositivity was not associated with the mortality or functional outcome (mRS) at one year.

5.2.2 Quality of life after stroke (IV)

Of the study population, 81 patients out of 147 were still in the study after six months. Mortality in the first six months was 52 patients and 14 patients had absconded. The majority of patients were men (58%). The mean age of patients was 54±16 years. Majority of patients were married (69%), 15% were widowed, and the rest were single or separated. As at the start of the SOMA-study, most surviving patients (67%) had ischemic stroke.

Relocating after stroke primarily from urban to rural areas affected 22% of the study population. Mainly men (68%) returned back to their previous occupation. They were younger than other patients (47±15 years), but the two eldest returnees were 82-year-old and 79-year-old females.

NEWSQOL interview was conducted with 31% of the patients at the 6-month (18 patients) or 12-month (7 patients) visits. The main causes for exclusion were severity of index stroke (23 patients), no follow-up due to moving further away (15 patients), or non-availability of Chichewa-speaking interviewer or interpreter at the time (14 patients). Thus, the patients who completed the NEWSQOL had less severe stroke, 48% vs 20% with mNIHSS 0-6 (χ^2 for mNIHSS 0-6 vs mNIHSS ≥7 =6.84, p=0.009), and better functional outcome, 80% vs 52% with mRS 0-2 (χ^2 for mRS 0-2 vs mRS ≥ 3 =6.29, p=0.012), in 6-month follow-up compared to those who did not have the interview.

Despite being HI -seropositive, stroke severity at presentation or the civil status did not affect any domains of the QOL subgroup analysis.

The mean scores for all domains were between 70 and 86 of the total score of 100. Patients with lower mRS at six months scored expectedly lower in the domains of ADL/self-care (95% CI -0.793 vs -0.238, p=0.0024) and communication (95% CI -0.707 vs -0.0453, p=0.0307) domains. Also as expected older age was associated with a worse QOL in the domain of ADL (95% CI -0.744 vs -0.122, p=0.0122). Females scored significantly lower than men in the domains of cognition (females

mean 67 ± SEM 8.5 vs males mean 85 ± SEM 4.4, p=0.05) and fatigue (females mean 63 ± SEM 9.8 vs males mean 91 ± SEM 2.9, p=0.01). The other domains: sleep, relationships, vision, and pain were not affected by any of the variables under investigation.

5.3 COMPARISON OF THE CHARACTERISTICS AND OUTCOME BETWEEN YOUNG STROKE PATIENTS IN MALAWI AND FINLAND (I, II, III)

Table 4 describes the characteristics and outcome of the study populations in the studies I, II and III. From the SOMA study (III) only the young stroke patients are included, the same age group, 18-49 years, which is comparable to the HYSR subjects. Malawian young stroke patients were relatively younger than their Finnish counterparts. HIV was prevalent amongst the Malawian young patients. They had more severe strokes. High leukocyte count was more common among the HYSR subjects. Hypertension was the most common conventional risk factor. Smoking, obesity, and hypercholesterolemia were more common amongst the Finnish stroke patients.

Table 4. The characteristics of young stroke patients and outcome of stroke in Malawi and Finland.

Item / unit	SOMA (n=46) Study III	HYSR (n=781) Study I	HYSR (n=681) Study II
age / years mean±SD	35.0 ± 7.7	41.4 ± 7.6	41.4 ± 7.6
Males / %	52.2	62.1	62.3
NIHSS / median (range)	11 (0 – 29)	3 (0 - 35)	3 (0-35)
Tax / °C mean ± SD	37.0 ± 1.0 (n=45)	36.6 ± 0.6	36.6 ± 0.6
s-leuk / mean ± SD	6.0 ± 3.1 (n=36)	8.9 ± 3.1	8.9 ± 4.0
HIV / %	73.9	0	0.1
Hypertension / %	22.7 (n=44)	38.8	37.4
DM / %	8.7 (n=43)	10.1	10.3
Chol / %	13.0 (n=36)	58.9	58.4
Smoking / %	11.1 (n= 45)	43.7	43.9
heavy drinking / %	13.3 (n=45)	14.5	14.8
obesity BMI/MUAC %	2.2	11.4	11.0
underweight/MUAC %	21.7	NA	NA
PI / %	28.2	13.3	10.3
PSI / %	15.2	NA	15.1
mRS 0-1 at 3 months / %	8.7	47.9	47.3
mRS 2-6 at 3 months %	78.3	52.1	52.7
Death (mRS=6) at 3 months %	10.9	4.2	3.5
mRS NA at 3 months %	13.0	0	0

N indicates the number of patients and is marked if it is different than the whole study group. NA indicates the non-availability of the information. In heavy drinking: observe the different definitions in Finnish and Malawian studies.

5.4 LONG-TERM FUNCTIONAL OUTCOME OF HIV SEROPOSITIVE PATIENTS (V)

The number of HIV seropositive patients that were managed in the outpatient clinic of Aurora increased from 98 in 1986 to 248 in 1991. Following screening and exclusions we included 80 patients in our study from 1986-1990. Mainly due to high mortality rate 23 patients were re-investigated during 1997 and only 17 were evaluated in the year 2013. All the followed patients were men and their median age in 2013 was 59 (range 46-75) years. They had high level of education, mean time of formal studies being 13 years. Alcohol abuse was an exclusion criteria in the beginning of the screening and none of these HIV seropositive men had increased their drinking in subsequent years. Smoking was a habit amongst seven patients and one patient admitted smoking marijuana occasionally. Fatigue (FSS >37) was found in nine patients according to the fatigue severity scale. Depression was diagnosed and treated in four patients. BDI – results did not vary during the times of examination: results were 4.65, 5.53, and 5.00, respectively indicating mild depressive symptoms. Hypertension was medicated and treated in five men; diabetes was diagnosed in two subjects. Nephropathy was also diagnosed in two patients, one caused by diabetes and the other by prostatic hyperplasia. Hypercholesterolemia was diagnosed and medicated in 11 patients.

The HIV seropositive men estimated that the time of infection occurred 28 (range 23-31) years ago. Most of them were infected through homosexual contact. None of the patients were iv-drug abusers. The median time from diagnosis of HIV was 27 (23-30) years. The median of blood CD4 count measured during the first year from diagnosis was within normal reference range: 680 cells/mm^3 (range 29-870 cells/mm^3). Low nadir CD4 level (<200 cells/mm^3) was found in 11 patients. The AIDS-defining disease was found in three patients, all before the start of cART. At present they all have cART, the median years on the cART being 13 (5-17) years. More than half of the patients had had cART for more than 10 years with successful continuous virological suppression. Altogether the study population had used antiretrovirals for 19 (9-24) years. None of the participants had antibodies against hepatitis C virus. HBcAb was positive in five patients indicating that they have had earlier hepatitis B infection while none of the patients had reactive HBsAg which would mean being a carrier of the virus. One patient was treated for syphilis due to positive serology (TPHA = 640, cardiolipins = 4)

In the neurological evaluation the EDSS median was 2.0 (range 1.0-4.0) indicating minimal disability. Four of the patients had a diagnosis of neuropathy. On the neurological examination these four and one additional patient had signs of neuropathy (Sensory FS 3.0-4.0). Moderate disability was also found in one patient, who had mild extrapyramidal signs and bladder dysfunction that increased his EDSS. None of the patients had loss of vision, cerebellar ataxia, prominent pyramidal

symptoms or other clinical signs of central nervous system abnormalities. They were all fully ambulatory. Most of the patients (16) had intact sensation of smell.

The neuropsychological results indicate changes especially between 1997 and 2013. All of these changes are typical for the aging brain: visuospatial processing weakens, memory functions worsen and the ability for speed and flexibility decreases.

The results of neuroimaging in 1997 and 2013 were compared: one patient had developed white matter changes indicating vascular degeneration or small vessel disease in the brain parenchyma (change of grade 1 to grade 2 in Fazekas scale). He also had lacunar infarctions and microbleeds in brain. One patient had signs of lacunar infarct already in 1997. Another patient had one lacunar infarction in 1997 and now had another one. None of these patients had had CNS symptoms or signs of stroke in their history. Four subjects had nonspecific T2-signal enhancements. Two patients had increasing atrophy in the brain one of which was measured the bicaudate ratio: 0.12 – 0.13 cm and the other measured the width of the third ventricle: 0.57 – 0.68 cm. Completely normal brain parenchyma was found in seven patients. One patient refused the MRI.

6 DISCUSSION

6.1 THE EFFECT OF INFECTIONS ON THE OUTCOME OF YOUNG STROKE VICTIMS (I, II)

In our young Finnish patients with acute stroke, the mean leukocyte count was above the laboratory reference range, thus, high leukocyte count was common. In the elderly stroke patients, high leukocyte count was associated with an unfavorable outcome.[123] In our investigation, the prevalence of infections before the event of stroke and after the stroke were 10% and 15%, respectively. In previous studies of PI and young stroke victims (under 50 years), the frequency is higher than in ours: 39%.[100,211] In the study of Grau et al, the prevalence of PI was markedly lower in the patients older than 50-years.[211] The higher leukocyte count, PI, and PSI all caused unfavorable 3-month outcome in our young patients with stroke. Only the infections after stroke affected the long-term mortality and risk of vascular events. There is strong evidence that PSI worsens the prognosis of acute stroke in elderly study populations from previous studies.[113-115,212] Symptomatic atherosclerosis is uncommon in young stroke patients, but its pathogenesis starts already at a young age. Some atherosclerotic findings are prevalent in arteries already in young stroke victims and the stroke risk starts to increase at early middle age.[213] Inflammatory processes can cause ischemic stroke.[93,94,99,100,106] Existing intracranial atherosclerosis may disturb the salvage of penumbra of ischemic lesion. Even in healthy children it has been observed that infection, even a mild one, can cause endothelial dysfunction.[104] This could explain why infections can trigger stroke in patients without overt atherosclerotic pathogenesis. In our study, higher leukocyte count was associated in exploratory multiple regression to dyslipidemia, smoking, and peripheral arterial disease (atherosclerosis). Low rate of atherosclerosis could explain why high leukocyte count was not predicting long-term poor outcome.[13,22,44]

Arterial dissection is the most common cause of stroke in the young.[22,24,44] It might be caused by vessel wall inflammation that is triggered by PI. These patients might even have a more generalized inflammatory process in their arterial endothelium leading to arteriopathy.[49] Further conventional risk factors, such as dyslipidemia, hypertension, and smoking activate the inflammation, cause increased levels of leukocytes, and activate the monocytes leading to endothelial inflammation.[42,43,214] Endothelium of the arteries is also part of the neurovascular unit that plays a part in regulating the inflammation in ischemic stroke.[215] This dysfunction of endothelium could partly explain the lower odds of good short-term recovery in our patients with PI or high leukocyte count. PI did not affect the long-term outcome, which is

likely due to the transient nature of often banal acute upper respiratory infection that only acts as a trigger of stroke.

The association between the higher leukocyte count and increased stroke severity or larger infarct size is, as shown in our study, a known finding also in previous investigations with the elderly population.[43,121,122,125,127,216] Ischemic lesion causes a strong inflammatory reaction that can increase the leukocyte count in the blood.[43,93,121,125,127,216-218] The larger lesion size causing inflammation partly explains why the high leukocyte count at the acute phase of ischemic stroke is predicting a poor outcome at three months.

There is solid evidence that PSI is linked with the unfavorable outcome.[113-115,212] Our study confirms this finding also in the young stroke victims. PSI was more frequent in patients with more severe stroke symptoms and larger lesion size also in our investigation.[110,111,219] Further, it was associated with other inflammatory parameters like the higher leukocyte count, CRP, and higher body temperature. It was the only inflammatory factor in this investigation that affected the long-term risk of vascular events and mortality. PSI like all other hospital acquired infections has a negative impact on prognosis of patients. Preventing these infections can improve the outcome of a stroke patient.

6.2 STROKE OUTCOME IN SUB-SAHARAN AFRICA (III, IV)

In Malawi, the conventional vascular risk factors were prevalent especially in patients who were older than 55 years of age. Hypertension was the most prevalent risk factor (55% of patients) as in many previous studies from the region.[72,75] DM was present in 20% of our patients and hypercholesterolemia in 15% of the patients. Compared to the general population of Malawi, the prevalence of increased blood pressure, glucose, and cholesterol were 32%, 6%, and 10%, respectively.[220] Obesity was as prevalent as in the general adult population in Malawi where 5.5% has BMI more than 30.[220] The rate of smoking and excessive drinking was slightly lower than expected according to the recent Malawian survey.

When the prevalence of the vascular risk factors is compared to other studies from SSA, the proportion of diabetic patients with stroke is higher than that reported in other research from the African region where the DM-prevalence was 0-15%.[75,221]

HIV infection was very prevalent in our younger stroke victims. The average age of HIV-infected stroke patients was 39.8 years. In many of them, stroke was the first indicator of the HIV infection, the WHO clinical signs of HIV infection were not present.[222] They had less severe strokes than the older study patients. Ischemic stroke was more common in this subgroup. Interestingly, four out of seven patients with atrial fibrillation (AF) were HIV-seropositive which could be a sign of HIV-

related cardiomyopathy in the older HIV-infected patients. In all, there is very scarce research about the relationship of stroke and infection in SSA.

Most (22 patients) HIV seropositive patients had low CD4 count indicating that they were eligible for the effective therapy (cART) according to the national program in Malawi.[223] However half of them did not start cART. Five patients had started cART within 5 months prior to their stroke. This could mean that the ischemic stroke was a sign of immune reconstitution inflammatory syndrome (IRIS) in these patients.[85] IRIS describes an inflammatory disorder associated with paradoxical worsening of pre-existing infectious processes following the initiation of cART. Few patients with cART had a CD4 count <100 cells/mm^3, suggesting a possible treatment failure. Some cART medication increases the possibility of vascular risk factors.[224]

The main determinants of an unfavorable 1-year outcome were the severity of stroke symptoms at the acute phase and the female gender. Our female patients did not have more prevalent AF, different acute therapy, or older age, which have been associated with the female stroke patients' worse prognosis in another investigation.[221] Most likely, in Malawi and some other resource-poor African countries, the socio-demographic factors can explain the unfavorable outcome in women with stroke.[71] Case-fatality is high when compared to European countries, but slightly lower when compared to other studies from SSA.[71] The severity of stroke on admission is usually higher than in the western world because in SSA people with mild stroke symptoms do not seek medical help or are not admitted to hospital. The medical system does not provide any outpatient follow-up or care. Family members, often women, play an essential role in vital issues such as with fluid and food intake, hygiene, and mobilization.

Our patients scored in NEWSQOL interview generally higher, meaning better QOL, than their European counterparts.[225,226] This could be explained by selection bias but also due to cultural differences. We found that female gender was negatively associated with QOL in the domains of cognition and fatigue. In other Sub-Saharan African studies from Nigeria, gender did not affect the post-stroke QOL.[89,90,227] The prevalence of post-stroke depression was higher in women in a South American study, and the depression was associated with disability and lower cognitive functioning.[228] In SSA, family participation in hospital and home care is essential for both survival and quality of life after stroke.

6.3 THE EFFECT OF LONG TERM HIV INFECTION IN SURVIVORS WITH BEST AVAILABLE THERAPY (V)

Development of cART and the patients' compliance with therapy help to preserve their neurological and neuropsychological capability. This study, following HIV-infected patients for three decades, revealed no significant signs of CNS impairment or development of HAND. Many of the results can be explained by normal aging. HIV affects the CNS in many ways.[229,230] The infected astrocytes can cause increase of glutamate-levels due to reduced uptake. The cells can also alter the blood-brain barrier more permeable and contribute to the generation of HIV reservoir in the CNS. The astrocytes can affect the non-infected astrocytes and destroy them through apoptosis. The latent CNS HIV infection and high levels of HIV in CNS is associated with HAND.

Since 1996 cART and viral suppression have been commonly available in Finland. Prior to then, our patients experienced mild or severe immunosuppression and even AIDS symptoms. Since most of our patients have been on the best available treatment for more than a decade, no symptoms of HAND emerged. Only neuropsychological examination can differentiate mild forms of HAND from early Alzheimer's disease.[182] One of our patients had some extrapyramidal signs, but apart from this, clinical examination found no CNS impairment. Extrapyramidal symptoms are rarely related to HIV infection. The only significant neurological impairment that was evident in our study population was peripheral neuropathy resulting from HIV infection itself, cART medication, or even diabetes in a few patients.[180]

In the USA, the CHARTER study investigating HIV seropositive patients found some signs of neuropsychological impairment in 52%, with even HAD emerging in 2%.[185] Of their 1555 subjects, 28% were using some recreational drugs. Our patients, however, did not use such drugs. This may in part explain the good outcome in our patients. The risk for HAND-like symptoms increases with co-infection with hepatitis C.[231,232] No-one in our study cohort had hepatitis C antigens. This can also explain their good neurocognitive outcome. Another benefit acting against development of neurocognitive diseases was that our study cohort individuals were well educated.

The prevalence of hypercholesterolemia amongst our patients can be explained by a well-known side-effect of antiretroviral medication, especially protease inhibitors.[149,233] The prevalence of other conventional risk factors for stroke was similar to that of the general population in Finland. That diabetes, hypertension, and hypercholesterolemia were treated appropriately also reduced risks for neurological and neurocognitive defects. Signs of silent strokes in MRI of our patients support general findings of an increase of the incidence of stroke in aging HIV population.[8,147]

6.4 FUTURE DIRECTIONS

In young stroke patients, who have less conventional risk factors, the contributing effect of infections may be more pronounced. A prospective study is needed, where the history of PIs is carefully checked from the stroke patients or their next-of-kin, and serology and plasma biomarkers of infections collected. Understanding and controlling the inflammatory processes and infections would help us to develop new treatments. This would help us to learn about the different stroke subtypes, including those young stroke victims with no overt cause of stroke. Could therapies against inflammation be neuroprotective during the phase of the first months after stroke? In a recently published trial, intravenous minocycline was a safe method but the sample size was too small to show efficacy.[234] According to the recent review and PASS-study, however, the preventative antibiotics immediately after stroke reduce the amount of PCIs but do not shorten the admission time or affect the outcome.[120] The researchers are discussing whether PCI is a sign of other condition causing unfavorable outcome and treating the PSI with antibiotics does not remove the 'hidden' cause. In rats, a drug called 3.6'-dithiotalidomide reduces the stroke size, reduces the inflammatory process, and improves the outcome.[235]

The prevalence of noncommunicable diseases is increasing in many Sub-Saharan countries.[68] In the treatment protocols and treatment possibilities, however, no development in same pace has occurred. In these countries, health budgets should prioritize the health education and treatment of hypertension, DM, and cessation of tobacco smoking. Malawi has a national program for cART access.[223] Despite this too many stroke patients are not on cART probably due to mobility problem caused by the stroke or not understanding for the need. We should understand that HIV infection could be an independent risk factor for ischemic stroke in young people. Patients with good compliance to cART, decent nutrition, and healthy lifestyle, can stay in proper cognition and condition even decades.

6.5 STRENGTHS AND LIMITATIONS OF OUR STUDIES

As far as we know, the Finnish HYSR studies (I and II) are the first ones to study the outcome of young stroke patients with infections. The study population is fairly large and well-investigated, and the follow-up is long. These studies are, however, retrospective covering almost a ten-year time period while the diagnostic methods and treatments of strokes have improved. Admission protocol omitted more detailed laboratory tests for inflammation, such as a high sensitivity-CRP or differential cell count of leukocytes. These studies were hospital-based, nevertheless, almost all young stroke patients from our catchment area are admitted and treated in HUCH.

In resource-limited countries like Malawi, patients do not come to any health facility when they develop stroke symptoms (III). Patients invariably stay home with mild stroke symptoms. Moreover those with the most severe strokes are kept at home. QECH has limitations with diagnostics and treatment. Equipment, including ECG or CT, was out of order without possibility of becoming functional within time frame of our study. We also lacked sufficient trained staff, such as Chichewa-speaking interviewer for our QOL study (IV). Due to these facts the QOL study selection became biased: some solely Chichewa speaking patients were not interviewed. One-year follow-up succeeded in most of our study patients (90%). Differences in in-hospital and one-year mortality compared to other studies from the region suggest: at the baseline our recruitment criteria was comparatively different and our stroke diagnosing was more meticulous.[71,76,77]

In Finland our study about long-term outcome of HIV infection the sample size is small in numbers (V). Before the onset of cART the disease was having a devastating effect. It may well be that our population of survivors represents a subgroup of HIV-1-infected persons who tolerate HIV-1 infection better than men in the average. Further, they were all well-educated and maintained good compliance throughout the years. Our study population might present a survival bias of the original population. On the other hand, the original study population represents prominent part of the HIV-infected population in Finland during 1980s. It is also the first study in the world as far as we know where HIV patients are followed-up for this length of time.

7 SUMMARY AND CONCLUSIONS

In our young stroke patients a common finding was high leukocyte count. Higher leukocyte count was independently associated after three months with a worse functional outcome. In the long-term follow-up, high leukocyte count had no association with the risks of future vascular events or mortality. Of our stroke population, 10% had a preceding infection and 15% developed an infection early on after the onset of stroke. According to our results, interestingly, both PI and PSI independently almost doubled the risk of an unfavorable 3-month outcome of stroke. Only PSI influenced the mortality or risk of vascular events after several years from stroke.

In the Sub-Saharan country of Malawi, the elderly stroke population commonly had conventional vascular risk factors present while young stroke victims were more often, without any other known risk factors, HIV seropositive. HIV infection did not affect the one-year outcome. The main determinants of an unfavorable outcome were severe symptoms of acute stroke and female gender. An effective treatment policy for non-communicable diseases in the countries of SSA would reduce significantly the risk of stroke. These countries have a unique opportunity to take the risk of increasing vascular diseases seriously and reduce the risk of stroke by acting accordingly through primary health care methods, and primary and secondary prevention. Improving the post-stroke care will reduce the case fatality and disability caused by stroke.

HIV seropositive men, even after the AIDS-phase, can recover and maintain their good health and cognition when they have the best available treatment, for longer than 25 years after the infection. The most significant neurological impairment was polyneuropathy. The results of the neuropsychological investigation only showed signs of normal aging. In conclusion our results give credence to the view that starting appropriate medication on time, delivering the therapy effectively, and taking care of other conditions that may threaten the brain, the HIV-infected persons may preserve their neurocognitive function. It would be interesting to do further investigations with the HIV-infected stroke patients: what are the related causes in the Finnish HIV population. Studies with high-quality data would guide us with the management of secondary prevention of vascular events, and long-term management of HIV-strokepatients.

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APPENDICES

APPENDIX 1. NEWSQOL

The 11 domains and 56 items of NEWSQOL

Domain	Item	Response options
Feelings		
	Do you feel less independent than you were, because of the stroke?	No, a little less, quite a lot less, very much less
	Has the stroke changed the way you feel about yourself?	No, a little, quite a lot, a great deal
	(If yes): And can I just check, would you say that the change is for the better or for the worse?	For the better, for the worse
	To what extent would you say your life has changed because of the stroke?	Not at all, a little, quite a lot, a great deal
	(If yes): And again, would you say that the change is for the better or for the worse?	For the better, for the worse
	Does the stroke make you feel useless at all?	No, a little useless, fairly useless, completely useless
	Do you feel you have less control over what is happening in your life because of the stroke?	No, a little less, a lot less, no control at all
	Do you feel depressed because of the stroke?	No, occasionally, sometimes, always
ADL/self-care		
	Because of the stroke, do you have difficulty preparing food, for example cutting a slice of bread or cutting up vegetables?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you have difficulty with housework because of the stroke?	No, some difficulty, a lot of difficulty, can't do it at all
	Because of the stroke, do you have difficulty with cooking?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you have difficulty managing the shopping because of the stroke?	No, some difficulty, a lot of difficulty, can't do it at all

	Because of the stroke, do you have difficulty using public transport (for example getting on and off, holding on to steady yourself)?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you have difficulty getting washed by yourself because of the stroke?	No, some difficulty, a lot of difficulty, can't do it at all
	Because of the stroke, do you have difficulty getting dressed by yourself, including things like zips and buttons?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you have difficulty getting in/out of the bath or shower on your own because of the stroke?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you find it difficult to concentrate for long because of the stroke?	No, a little difficult, quite difficult, very difficult
	Because of the stroke, are there times when you forget what you have said or what people say to you?	No, occasionally, sometimes, always
	Because of the stroke do you find it difficult to solve problems or make decisions?	No, a little difficult, quite difficult, very difficult
	Would you say you keep forgetting things because of the stroke?	No, occasionally, sometimes, always
	Because of the stroke, do you find it difficult to think clearly?	No, a little difficult, quite difficult, very difficult
Mobility		
	Because of the stroke, do you walk with a stick or frame or by holding onto things?	No, sometimes, always, can't walk
	Because of the stroke, do you have difficulty standing for any length of time?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you find that you are unsteady on your feet because of the stroke?	No, quite unsteady, very unsteady, can't stand
	Do you feel as if you walk slowly because of the stroke?	No, quite slowly, very slowly, can't walk
	Because of the stroke, do you have any difficulty walking half a mile	No, some difficulty, a lot of difficulty, can't do it at all
	Because of the stroke, do you have any difficulty walking up or down hills?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you have difficulty managing stairs on your own because of the stroke?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you have difficulty bending down because of the stroke?	No, some difficulty, a lot of difficulty, can't do it at all
	Do you get around in a wheelchair because of the stroke?	No, occasionally, sometimes, always

Emotion		
	Do you get more emotional because of the stroke?	No, a little more emotional, more emotional, quite a lot more emotional, very much more emotional
	Do you sometimes cry at the least thing because of the stroke?	No, occasionally, sometimes, always
	Are you worried that you could have another stroke?	No, a little worried, quite worried ,very worried
	Because of the stroke, do you worry about becoming dependent on other people?	No, worry a little, worry quite a lot, worry a great deal
Sleep		
	Do you have problems sleeping at night because of the stroke?	No, occasionally, sometimes, always
	Because of the stroke, do you sometimes wake up too early?	No, occasionally, sometimes, always
	Do you have difficulty getting off to sleep because of the stroke?	No, occasionally, sometimes, always
	Do you ever feel exhausted because of the stroke?	No, occasionally, sometimes, always
	Do you feel that you lack energy because of the stroke?	No, occasionally, sometimes, always
	Do you find you need a lot of rest because of the stroke?	No, occasionally, sometimes, always
Interpersonal relationships		
	Are you short-tempered because of the stroke?	No, a little short-tempered, quite short-tempered, very short-tempered
	Has the stroke put any strain on your relationship with your spouse or partner?	No, a little strain, quite a lot of strain, a great deal of strain
	Because of the stroke, do you argue more with close friends or family?	No, a little more often, a lot more often, argue all the time
	Are you less tolerant because of the stroke?	No, a little less tolerant, quite a lot less, very much less
	Does the stroke interfere with your sex life and if so, how much?	No, a little, quite a lot, a great deal
	Because of the stroke, have you become nervous about meeting people?	No, a little nervous, quite nervous, very nervous

Communication		
	Do you feel as though your speech is slurred at all because of the stroke?	No, a little slurred, quite slurred, very slurred
	Do you find it difficult to make yourself understood because of the stroke?	No, a little difficult, quite difficult, very difficult
	Because of the stroke, are there times when you have difficulty expressing yourself?	No, occasionally, sometimes, always
	Do you have any difficulty with writing because of the stroke?	No, some difficulty, a lot of difficulty, can't write at all
Pain/sensation		
	Do you have any pain because of the stroke?	No, a little pain, quite a bit of pain, a lot of pain
	How often do you have pain because of the stroke?	Never, occasionally, sometimes, often
	Because of the stroke, do you have difficulty picking up small things?	No, some difficulty, a lot of difficulty, can't write at all
Vision		
	Do you have problems with your eyesight because of the stroke?	No, slight problems, moderate problems, severe problems
	Do you have any difficulty with reading because of your eyesight (check: because of the stroke)?	No, some difficulty, a lot of difficulty, can't read at all
Fatigue		
	Do you doze off during the day because of the stroke?	No, occasionally, sometimes, always
	Because of the stroke, are there days when you feel you could sleep all the time?	No, occasionally, sometimes, always
	Because of the stroke, do you feel that you can't be bothered with things at times?	No, occasionally, sometimes, always

APPENDIX 2
FATIGUE SEVERITY SCALE ENGLISH AND FINNISH VERSIONS

Fatigue Severity Scale (FSS)

	Completely disagree						Completely agree
1. My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2. Exercise brings on my fatigue	1	2	3	4	5	6	7
3. I am easily fatigued	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
8. Fatigue is among my 3 disabling symptoms	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family or social life	1	2	3	4	5	6	7

Individuals are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each statement where 1 indicated strongly disagree and 7 strongly agree

Uupumusoire-asteikko

Tällä asteikolla arvioidaan uupumuksesi määrää. FSS on lyhyt kysely, jossa Sinun pitää arvioida uupumustasi.

FSS sisältää yhdeksän väitettä. Lue jokainen väite ja ympyröi joku numeroista 1-7, riippuen siitä, kuinka täsmällisesti se sopii vointiisi viimeisen viikon aikana ja oletko samaa tai eri mieltä toteamuksen kanssa.

- Numero yksi tarkoittaa että olet täysin eri mieltä väitteestä.
  Numero seitsemän tarkoittaa, että olet täysin samaa mieltä.
- Muista ympyröidä jokaisen väitteen kohdalla vain yksi numeroista.

FSS väitteet:

Viimeisen viikon aikana olen huomannut, että:

	Eri mieltä						Samaa mieltä
1. Motivaationi on alempi, kun olen uupunut.	1	2	3	4	5	6	7
2. Liikunta lisää uupumustani.	1	2	3	4	5	6	7
3. Uuvun helposti.	1	2	3	4	5	6	7
4. Uupumus alentaa toimintakykyäni.	1	2	3	4	5	6	7
5. Uupumus aiheuttaa minulle usein ongelmia.	1	2	3	4	5	6	7
6. Uupumus estää pitkäkestoisen fyysisen toiminnan.	1	2	3	4	5	6	7
7. Uupumus häiritsee tiettyjen tehtävieni hoitamista.	1	2	3	4	5	6	7
8. Uupumus on yksi kolmesta pahimmasta oireestani.	1	2	3	4	5	6	7
9. Uupumus häiritsee työ-, perhe-, tai sosiaalista elämääni.	1	2	3	4	5	6	7

Kokonaispisteet: /63